ADalimumab Vs. conventional ImmunoSupprEssion for uveitis (ADVISE) Trial

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ADVISE Protocol 1.3 (12 Oct 2020)
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Document revision history

Version 1.0 (6 Feb 2019)

- Cover: added ClinicalTrials.gov identifier

- Table 2: Visit and Examination Schedule: Added height at month zero (baseline)

- Table 4: Prednisone tapering schedule: 7.5 mg/day hold period modified from "Hold for 4 weeks" to "Hold until two study visits ≥4 weeks (28 days) apart have occurred*
  **Note: This may involve maintaining the dose for more than two consecutive study visits if they occur <28 days apart.*

- Corrected typographical errors, e.g., <7.5 mg/day prednisone to ≤ 7.5 mg/day in section 2.2 (secondary hypotheses #1 and 4.2.2 in description of primary outcome)

Version 1.1 (31 Oct 2019)

- Section 1.2 IND
  - Added clarification that the IND covers the conventional immunosuppressive drugs used in the trial

- Section 1.4 Resource centers
  - Updated the location of Study Chairman's Office (as of 1 Aug 2019)

- Section 3.1 Design elements
  - Corrected time points for masked assessment of photographic images and OCT by the RC (graders masked)
    - All patients
      - OCT at baseline, 3, 6, and 12 months
      - Retinal color photographs at baseline, 6 and 12 months
    - Disease-specific image or OCT, as applicable, at baseline, 1, 3, 6, and 12 months

- Section 3.2.1 Randomized treatment arms (Adalimumab)
  - Removed adalimumab dosing schedule for adolescents <30 kg (they are now excluded from the study)

- Section 3.4.3 Disease-specific assessment to permit ascertainment of outcomes pertaining to activity of uveitis
  - For birdshot chorioretinitis - corrected Humphrey 24-2 to 30-2
  - Removed "other conditions with exudative detachment(s)" from list of conditions for which OCT will be used to determine resolution of exudative detachments. Vogt-Koyanagi-Harada early disease is the only condition that will be monitored in that manner.

- Section 3.5 eligibility criteria
  - Added inclusion criterion: Weight 30 kg (66 lbs) or greater
  - Added exclusion criterion: Any of the following baseline lab values
    a. White blood count <3500 cells per microliter
    b. Platelets <100,000 per microliter
    c. Hematocrit <30%
    d. AST or ALT >1.5X upper limit normal value
    e. Serum creatinine >1.1X upper limit normal value
  - Expanded exclusion criterion "Multiple sclerosis' to "Multiple sclerosis or other demyelinating disease"
  - Added clarification regarding MRI screening as italicized: For patients with *anterior/intermediate* or intermediate *uveitis without systemic disease*, abnormal magnetic resonance imaging (MRI) of the brain consistent with demyelinating disease
  - Added exclusion criterion: Severe uncontrolled infection
  - Added exclusion criterion: Moderate to severe heart failure (NYHA class III/IV
  - Added exclusion criterion: Active malignancy
  - Expanded pregnancy exclusion and length of time birth control use required: *For persons of child-bearing potential or impregnating potential, unwillingness to use appropriate birth control (abstinence, combination barrier and spermicide, hormonal, or intrauterine device) for the next 15 months or plans to become a biological parent within the next 15 months*

- Section 3.7 Data collection table
  - Added note for disease specific test early-stage VKH, – OCT: ^ OCT centered on fovea and additionally, as needed, OCT centered to capture the area with greatest subretinal thickness
  - Removed *other conditions with exudative detachment(s)* from conditions for which OCT will be used to determine resolution of exudative detachments for determination of uveitis activity.
  - Added italicized clarification: Gadolinium enhanced MRI *for patients with anterior/intermediate or* intermediate uveitis *without systemic disease* only
  - Corrected parameter for automated perimetry with Humphrey SITA-fast 30-2 (previously 24-2 in error) and P60.

- Section 4. Treatment

  General modifications to section 4 and subparts:
  - Renamed section from Treatment schedule to Treatment
  - No essential changes made; generally reworked of sections for clarification including
    - Clarification that study treatments should adhere to guidelines. For situations not covered by guidelines, follow general study treatment principles and use best medical judgment
    - Specified basic principles for study treatment
    - Clarified that time points in treatment guidelines (e.g., 4 weeks) are targets and that variations due to scheduling of study visits is permitted and expected

- Section 4.2.1 Initial prednisone dose
  - Revised *Table 3: Initial prednisone dosing summary* to include more detail

- Section 4.3.1 Adalimumab treatment group
  - Removed dosing protocol for adolescent patients based on body weight (i.e., different dosing protocols for adolescents < 30 kg vs those ≥30 kg for which dosing protocol is same as for adults). Only patients ≥30 kg will be enrolled in trial, thus the same dosing protocol will be used for all patients.
  - Changed reference for adolescent dosing (previously referenced Sycamore study)

- Section 4.3.2 Conventional immunosuppression treatment group
  - *Table 5: Conventional immunosuppressive drugs in the ADVISE* Trial - revised footnote re: timing of dose escalation for tracrolimus from monthly to every 2 to 4 weeks

- Section 4.4 Advancement of immunosuppression – entire section was added

- Section 4.5 Management of uveitis reactivation
  - Section reworked for reactivation for clarity with the addition of some details including specification of prednisone dose to be reinstated if uveitis reactivates after achieving cessation
  - *Table 6. Reactivation management guidelines* was revised to two tables, 6a and 6b, for prednisone and immunosuppression, respectively

- Section 9.1 Recruitment and informed consent
  - Added clarification that adolescent participants and parent or guardian will give written assent/consent according to the guidelines of the clinic's governing IRB.
  - Changed reading level of consent from 8th grade level to 9th grade level

- Section 10.2.2 Visual Function Quality Assurance Committee
  - Corrected Humphrey 24-2 to 30-2

- References
  - Removed: Ramanan AV, Dick AD, Jones AP, McKay A, Williamson P, Compeyrot-Lacassagne S, Hardwick B, Hickey H, Hughes D, Woo P, Benton D, Edelsten C, Beresford M for the SYCAMORE Study Group. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med 2017;376:1637-46. PMID: 28445959

- Corrected typographical and spelling errors throughout

Version 1.2 (13 Dec 2019)

- Section 3.1 Design elements, added: First patient enrolled in September 2019; the end of the trial (completion of follow-up of last patient enrolled) is expected to be February 2023.

- Section 3.5 Eligibility criteria
  - Added the following clarification to exclusion criterion Untreated active hepatits B or C infection: *Active hepatitis B is defined as positive surface antigen; active*

hepatitis C is defined as positive antibody and positive polymerase chain reaction (PCR)
- Added exclusion: Receipt of a live vaccine within past 30 days
- Added exclusion: Hypersensitivity to any of the study treatments or their excipients
- For exclusion re: unwillingness to use birth control for persons of child-bearing or impregnating potential:
  - Changed time for use of birth control from 15 to 18 months
  - Added note that combination barrier and spermicide should not be used by UK patients

- Section 6. Possible side effects and complications of study treatments
  Added medications that are prohibited during the trial for safety reasons:
  - Live vaccines
  - Substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP), e.g., bosentan, dabigatran etexilate and aliskiren.
  - Products containing Hypericum perforatum (St John´s Wort) to avoid risk of interaction with tacrolimus (also added to tacrolimus entry in Table 7, Potential risks of therapy

- Section 7.2 Serious adverse events: Specified that UK clinics are required to report SAEs to the CC within 24 hours as to be compliant with EU/UK requirements. Non-UK clinics have 72 hours to report SAEs to the CC.

Version 1.3 (9 Oct 2020)

- Section 3.7 Data collection schedule, Table 1 Visit and examination schedule
  - Added clarification to footnote: chemistry panel including serum glucose
  - Added clarification: Screening P-60 test

- Section 3.4.3 Disease-specific assessment to permit ascertainment of outcomes pertaining to activity of uveitis: Birdshot chorioretinitis – Corrected Humphry settings by changing 24-2 to 30-2 in two places as missed during

- Section 4.2 Systemic corticosteroids: Corrected typo in first paragraph, maximum dose of prednisone; changed 60 mg/kg/day to 60 mg/day

- Section 4.2.1 Initial prednisone dose, Table 3. Initial prednisone dosing summary: Added text (as italicized) to scenarios “substantively improved “and “not controlled” in last column: Taper *but not below 7.5 mg/day until inactive*

- Section 4.5 Management of uveitis reactivation, Table 6a, Reactivation guidelines – Prednisone: Added italicized text for clarification for scenario, Reactivation during prednisone taper -Not controlled, 4 weeks after prednisone increase*:* Taper *but not below 7.5 mg/day until inactive*

- Section 4.8.1 Regional corticosteroid Injections: Revised to make the intravitreal dexamethasone pellet an acceptable ancillary treatments for macular edema. Previously treatment with the dexamethasone pellet was excluded because, at the time the protocol was written, the expected duration of the treatment effect was about 5 months based on data from the HURON Trial. However, in the POINT Trial we found the treatment effect to be shorter, about the same as Triesence, approximately 3 months.

- Section 4.8.2 Topical corticosteroids
  - Corrected typo in the concentration of difluprednate from 0.005 to 0.05
  - In 3rd bullet, clarified the maintenance dose permitted for each of three drugs

- References: Added reference 74 (results of POINT Trial)

Document distribution

Version	Version date	Distribution	Distribution date
1.0	26 Oct 2018	Abbvie JHSPH IRB	29 Oct 2018 06 Nov 2018
	19 Dec 2018	JHSPH IRB Clinical Centers FDA	28 Dec 2018 24 Jan 2019 (PPM 1) 06 Feb 2019
	06 Feb 2019*	JHSPH IRB	8 Feb 2019
1.0 Canada†	30 Oct 2019	Health Canada MUHC clinical center	30 Oct 2019 04 Nov 2019
1.0 UK‡	22 Nov 2019	UK Medicines and Healthcare products Regulatory Agency (MHRA)	28 Nov 2019
1.1	31 Oct 2019*	JHSPH IRB	5 Nov 2019
1.2	13 Dec 2019	JHSPH IRB Clinical Centers FDA Health Canada	16 Dec2019 31 Jan 2020 (PPM 21)\ 05 Jun 2020 12 Mar 2020
1.3	12 Oct 2020		

* Interim versions, not distributed to clinical centers

† Interim Canadian version only (19 Dec 2018 to 30 Oct 2019): Revisions requested by Health Canada were made to this Canadian-only version. The following exclusion criteria were added: severe uncontrolled infection; moderate to severe heart failure (NYHA class III/IV); active malignancy. Subsequently these revisions were incorporated into protocol version 1.2 (13 Dec 2019.

‡ Interim UK only version (19 Dec 2019 to 22 Nov): Revisions requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA) were made to this UK version. These are the substantive changes made to exclusion criteria: clarification of lab results for active hepatitis B and C infections; added exclusion for specificed baseline lab values; added exclusions for severe uncontrolled infection, live vaccine within past 30 days,hypersensitivity to and study treatments or excipients; revision of pregnancy criteria to include persons of child-bearing or impregnating potential. Added medications not to be used during the trial (end of section 6.). Subsequently these revisions were incorporated into protocol version 1.2 (13 Dec 2019).

Abstract

The uveitides are a collection of diseases characterized by intraocular inflammation. Collectively, they are the 5th leading cause of blindness in the US, and the estimated cost of treating them is similar to that of treating diabetic retinopathy. Non-infectious intermediate, posterior, and panuveitides have the highest rates of visual loss and typically are treated with oral corticosteroids and immunosuppression. The Multicenter Uveitis Steroid Treatment (MUST) Trial (a randomized, comparative effectiveness trial, which compared 2 treatment paradigms for these diseases, systemic therapy with corticosteroids and immunosuppression vs. regional therapy [the fluocinolone acetonide implant]), and Follow-up Study demonstrated the superiority of the systemic approach to the regional ocular approach in terms of long-term visual outcomes with essentially no increase in systemic side effects in the systemic group. One key to systemic therapy's success was the use of systemic immunosuppression in 88% of participants, coupled with tapering the prednisone to ≤7.5 mg/day, a relatively safe dose. Non-alklyating agents are typically the first choice and the most often used are azathioprine, methotrexate, mycophenolate, cyclosporine, and tacrolimus. The alkylating agents, cyclophosphamide and chlorambucil, are used less often because of concerns about potential increased malignancy risk. Data from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study suggest that each of the conventional, non-alkylating agent immunosuppressive drugs is effective in controlling the inflammation while permitting tapering prednisone in ~40-55% of patients; hence combination therapy often is needed. Furthermore, minimizing the daily dose of prednisone is important, as the risk of cardiovascular disease and mortality increase with the cumulative dose of oral corticosteroids. In June 2016, the fully-human, anti-TNF-α monoclonal antibody, adalimumab, was approved by the US Food and Drug Administration (FDA) for the treatment of uveitis. Anti-TNF-α monoclonal antibody therapy has revolutionized the management of the rheumatic diseases largely due to its superior efficacy compared to conventional Disease Modifying Anti-Rheumatic Drugs. Data from VISUAL III, the extension of the two phase 3 trials that led to the FDA approval of adalimumab for the treatment of uveitis, suggest that adalimumab may be superior to conventional immunosuppression, as ~75% of participants had controlled inflammation with prednisone doses ≤5 mg/day. The ADalimumab Vs. conventional ImmunoSupprEssion for uveitis (ADVISE) Trial is a randomized, comparative effectiveness trial comparing adalimumab to conventional agent immunosuppression for patients with non-infectious, intermediate, posterior, and panuveitides. The primary outcome is the ability to successfully taper prednisone to ≤7.5 mg/day by 6 months after randomization while maintaining control of the inflammation. Secondary outcomes include prednisone discontinuation by 1 year, visual acuity, and complications of uveitis and its treatment.

1. Introduction

1.1 Title

ADalimumab Vs. conventional ImmunoSupprEssion for corticosteroid-sparing for uveitis (ADVISE) Trial

1.2 IND

ADVISE is being conducted under IND 132532 held by Jennifer E. Thorne, MD, PhD, the Study Medical Safety Officer, for the Coordinating Center. The product named in the IND is Humira (adalimumab); the IND covers the conventional immunosuppressive drugs used in ADVISE (i.e., azathioprine, methotrexate, mycophenolate, cyclosporine, tacrolimus).

Adalimumab was FDA approved for the treatment of non-infectious intermediate, posterior, and panuveitides in adult patients in 2016 and in pediatric patients 2 years of age and older in 2018. In 2016, prior to FDA approval of adalimumab for treatment of uveitis in pediatric patients, the Coordinating Center submitted an IND exemption request to the FDA for use of adalimumab in adolescent patients (13 to <18 years of age) for the ADVISE Trial. In response, the FDA determined that use of adalimumab for the treatment of non-infectious intermediate, posterior, and panuveitides in adolescent patients in ADVISE does not increase risk for these patients as the drug was approved for treatment of pediatric patients for other indications. However, although conventional immunosuppressive drugs are the standard approach and in widespread use, these drugs are not FDA approved for treatment of non-infectious intermediate, posterior, and panuveitides, and therefore an IND is required.

1.3 Financial sponsor

ADVISE is funded by the National Eye Institute through linked UG1 grants to the Study Chairman's Office (CO), the Coordinating Center (CC), and the Reading Center (RC). Clinical centers are funded through sub-agreements with the CC.

1.4 Resource centers

Center	*Director/Co-Directors*
Study Chairman's Office Johns Hopkins Bloomberg School of Public Health, Baltimore	Douglas Jabs, MD, MBA
Coordinating Center Johns Hopkins Bloomberg School of Public Health, Baltimore, MD	Janet Holbrook, PhD, MPH Elizabeth Sugar, PhD
Reading Center University of Wisconsin at Madison, Madison, WI	Michael Altaweel, MD

1.5 Clinical centers

Clinical centers will be located in the United States, the United Kingdom, Australia, and Canada. A list of participating clinical centers is included in the ADVISE Manual of Procedures.

1.6 Additional Support

AbbVie (Chicago, IL) will donate adalimumab for the trial.

1.7 Background and significance

The uveitides are a collection of diseases characterized by intraocular inflammation.[1] In the United States (US), the uveitides collectively are the 5th leading cause of blindness and are responsible for an estimated 30,000 new cases of blindness annually.[2] They cause an estimated 2.8% to 10% of blindness in the working age population.[2,3,4,5,6] The cost of treating the uveitides is comparable to that of treating diabetic retinopathy.[7] In addition to the estimated direct cost of treatment, there are substantial indirect costs, as treatment of the more severe uveitides is labor intensive, typically requiring patient visits every 4-6 weeks for at least several years. The estimated incidence of uveitis is 17-54/100,000/year, and the estimated prevalence of active uveitis is 115-204/100,000.[3,5] In 1993, Research to Prevent Blindness estimated the prevalence as 1% of the US population.[8] Because the uveitides affect all ages, including children and working-age adults, the potential years of vision lost and economic impact per case exceed that of age-related diseases, such as cataract and age-related macular degeneration. Hence research into improving the outcomes of management of these diseases is critical for lessening their burden of visual impairment and blindness. For these reasons, improving methods for the treatment of the uveitides is one of the strategic goals of the National Plan for Eye and Vision Research (htpps://nei.nih.gov/strategicplanning/np_retinal, accessed 30 August 2016).

The uveitides typically are classified by the primary site of inflammation as anterior, intermediate, posterior, or panuveitis.[1,9] Although anterior uveitides are somewhat more common than intermediate, posterior, or panuveitides, the incidences of visual impairment (worse than 20/40) and blindness (20/200 or worse) are far greater among intermediate, posterior and panuveitides. For posterior and panuveitides, the rates of visual impairment and blindness are nearly 3-fold greater than those seen with anterior uveitides.[10] Hence intermediate, posterior, and panuveitides cause a disproportionately large share of visual impairment and blindness from uveitis. Uveitides may be infectious or non-infectious; the majority of cases in the US are non-infectious.[1,9] Uveitides also may be monophasic and spontaneously-remitting, recurrent acute (episodic with periods of inactive disease off treatment between attacks), or chronic (with prompt relapse upon discontinuation of treatment and the need for chronic suppression). The large majority of cases of intermediate, posterior, and panuveitides are chronic and require long-term, possibly life-long, therapy.[1,9] Although some cases of intermediate uveitis may be observed or treated intermittently,[11,12] many cases of intermediate uveitis and nearly all posterior and panuveitides require treatment with oral corticosteroids and immunosuppression.[13,14,15,16] Immunosuppressive drug treatment provides superior outcomes to corticosteroids alone for several specific uveitic diseases.[15,17,18,19,20] In the MUST Trial and Follow-up Study, systemic therapy with oral corticosteroids and immunosuppression produced superior visual acuity outcomes at 7 years of follow-up compared to regional therapy with the fluocinolone acetonide intraocular implant, in part due to the variable duration of effect of regional therapies and the uveitis reactivation that occurs prior to re-implantation.[15] Furthermore, the systemic approach had a significantly lower risk of ocular adverse effects (primarily cataract and ocular hypertension/glaucoma) with no significantly increased risk of systemic side effects, except for a greater use of antibiotics for infections.[15,21,22,23,24] Sustained, drug-free, remissions (defined as inactive disease off all treatment) occasionally are possible for some chronic uveitides managed with immunosuppression, but they are infrequent.[15,25,26,27] The Systemic Immunosuppressive Therapy for Eye Disease (SITE) Cohort Study estimated the drug-free remission rate in intermediate uveitis at 8.6%/person-year (PY).25 In juvenile idiopathic arthritis (JIA)-associated chronic uveitis, the median time to a drug-free remission for mild disease is ~10 years, and only

~25% of those with severe disease ever achieve a remission.[26,27] The Mount Sinai Multifocal Choroidopathy Study reported that no patients with these posterior uveitides were in drug-free remissions at 2 years of follow-up, and only 11% were able to discontinue prednisone successfully, despite the use of immunosuppression in all patients.[16] The SITE Cohort Study estimated the rate of drug-free remissions for each non-alkylating agent immunosuppressive drug at 5 to 9%/PY.[28,29,30,31] In the MUST Trial and Follow-up Study, only ~25% of participants treated with systemic therapy were in drug-free remissions at 7 years of follow-up.[15] Hence long-term, chronic therapy with oral corticosteroids and/or immunosuppression typically is needed to control these diseases and preserve vision.

Oral corticosteroids and immunosuppression have the potential for systemic side effects, but most are reversible with dose reduction or discontinuation of the appropriate agent.[13,14] In the MUST Trial and Follow-up Study, there was no significant increase in systemic adverse effects through 7 years of follow-up among those assigned to systemic therapy versus those assigned to treatment with a regional, intraocular therapy (the fluocinolone acetonide implant) with the one exception. Those assigned to systemic therapy were more likely to be given antibiotics for infections.[15,21,22,24] A key to the successful management of this systemic approach is tapering prednisone to relatively safe doses. Meta-analyses of trials in rheumatoid arthritis have shown that prednisone at a dose of $\leq$7.5 mg/day appears safe for the intermediate-term (~ 2 years),[32] and in the MUST Trial and Follow-up Study (in which minimal systemic side effects occurred), the median dose of prednisone among those still on prednisone at 7 years of follow-up was 6.25 mg/day.[15] However, long-term studies of patients with rheumatoid arthritis demonstrate that the risks of overall and cardiovascular mortality both increase with the cumulative dose of prednisone,[33] suggesting that efforts must be made to discontinue or at least minimize the daily dose of oral corticosteroids. Although doses of prednisone of 5 to 7.5 mg/day might be tolerated for years, they cannot be used indefinitely, due to the increased risk of cardiovascular disease.[33] Improved corticosteroid-sparing immunosuppression among uveitis patients is critical to minimizing the use of systemic corticosteroids and improving patients' long-term outcomes given that long-term, potentially life-long, treatment may be required and the relatively low rate of remission.[14]

Immunosuppressive drugs include small molecules (conventional agents) and biologic agents. The principal small molecule immunosuppressive drugs include the antimetabolites, azathioprine, methotrexate, and mycophenolate; the calcineurin inhibitors, cyclosporine and tacrolimus; and the alkylating agents, cyclophosphamide and chlorambucil.[14,28,29,30,31,34,35,36] The biologic agents most often used for treatment of the uveitides are anti-tumor necrosis factor (TNF)-α monoclonal antibodies (e.g., infliximab, adalimumab), although there are case reports and small case series with other agents.[37,38,39,40,41,42] In the MUST Trial and Follow-up Study, 88% of participants assigned to systemic therapy received immunosuppression; all of these patients received conventional immunosuppression as the initial agent. Currently, the majority of patients with uveitis receiving immunosuppression are treated with antimetabolites or calcineurin inhibitors. Alkylating agents may be more effective,[34] but their use has been curtailed due to their increased cancer risk.[43,44,45,46,47] Biologic agents also have been used less often in the past, in part due to restricted access in the US prior to US FDA approval for uveitis. Data from the SITE Cohort Study suggest that antimetabolites and calcineurin inhibitors, when used as the only immunosuppression agent, are effective in controlling the inflammation and allowing tapering of prednisone to $\leq$10 mg/day in ~40-55% of patients by 6 months of treatment.[28,29,30,31] As such, dose escalation of immunosuppressive agents, switching agents, and combination therapies (e.g., an antimetabolite with a calcineurin inhibitor) commonly are needed.[14,16] When uveitis reactivation occurs, the dose of prednisone is increased until the

uveitis is inactive again and the prednisone taper resumed, sometimes more slowly, increasing the cumulative exposure to oral corticosteroids and the potential for side effects.

In June 2016, adalimumab (Humira®, AbbVie, Chicago, IL), a fully human monoclonal antibody to TNF-α, administered subcutaneously, was approved by both the US FDA and by the European Commission for the treatment of noninfectious, intermediate, posterior, and panuveitides. These approvals were based on two industry-sponsored, randomized, placebo-controlled, double masked, drug-licensing trials comparing adalimumab versus placebo for patients with active and inactive uveitis (VISUAL I and II, respectively). These trials demonstrated the superiority of adalimumab over placebo by prolonging the time to treatment failure (uveitis relapse) among participants on a rapid corticosteroid taper to discontinuation.[37,38] In the VISUAL III treatment extension study participants were permitted to use low-dose oral corticosteroids. In VISUAL III, ~75% of patients had inactive uveitis with a prednisone dose ≤5mg/day, beginning at 11 weeks after entry and continued through at least 1 year of follow-up. Furthermore, in VISUAL III, the mean dose of prednisone over time was 2 mg/day. (Douglas, Kevin, AbbVie, personal communication, 2017). These data suggest that adalimumab may be superior to conventional immunosuppression as corticosteroid-sparing therapy (success rates of ~40 to 55% in the SITE Cohort Study[28,29,30,31] and long-term mean doses of prednisone of 5-6 mg/day in the both Mount Sinai Multifocal Choroidopathy Study and the MUST Trial Follow-up Study[15,16]). A recently-published, randomized, placebo-controlled clinical trial of adalimumab added to methotrexate demonstrated its efficacy in managing JIA-associated uveitis in children. Furthermore, aside from an increased risk of infection (also seen with conventional immunosuppression in the MUST Trial and Follow-up Study) and injection site reactions, adalimumab appears relatively safe for long-term use.[48,49,50] Although the initial SITE Cohort Study publication suggested a possible increased risk of malignancy with anti-TNF biologic agents,[45] these data were from a very small sample size, and sensitivity analyses of the estimates were unstable. Large observational databases[48,49] and meta-analyses[50] have demonstrated no increased risk of malignancies with anti-TNF treatment, except possibly non-melanoma skin cancer, a risk also sometimes reported with conventional, small molecule immunosuppression.[46] The potential superiority as a corticosteroid-sparing agent and apparently similar safety of adalimumab to conventional immunosuppressive agents suggest the need for a randomized, comparative effectiveness trial comparing adalimumab to conventional immunosuppression for the treatment of non-infectious, intermediate, posterior, and panuveitides.

A key feature in the management of the uveitides is successful control of the inflammation.[51,52,53] When evaluated using time-updated methodology, the presence of any inflammation increases the risks of visual impairment and blindness by 2- and 3-fold, respectively, and there appears to be a dose-response effect with greater inflammation resulting in higher risks of visual impairment and blindness.[51,52,53] Therefore, the definition of treatment success for corticosteroid-sparing includes tapering prednisone to ≤7.5 gm/day while maintaining inactive disease.[9,16,32] Measurement of uveitis control varies by specific disease. For example, for intermediate uveitis, vitreous haze is a good measure of activity (and has been used for US FDA drug approval of Ozurdex®),[9,54] but for serpiginous choroiditis it is not, as there is no vitritis with serpiginous. For serpiginous choroiditis, multimodal imaging has demonstrated that fundus autofluorescence (FAF) correlates well with disease activity, and it has become the standard method for following such patients.[55] Similarly, for birdshot chorioretinitis (BSCR), vitreous haze typically is mild, and FAF is not helpful, but prevention of loss of peripheral visual field (and sometimes reversal of loss) from active disease is an important measure.[17,18,55] To address this heterogeneity, the ADVISE Trial will use disease-specific assessments for

determining active vs. inactive disease in each participant (see Table 2. Visit and Examination Schedule in section 3.7 below and the Guidelines for Determining Inactive Disease in the ADVISE Manual of Procedures).

1.8 Preliminary studies

The MUST Trial and Follow-up Study compared the fluocinolone acetonide intraocular implant (a strictly regional corticosteroid approach, designed to last 3 years, with re-implantation as needed) to systemic therapy with oral corticosteroids and immunosuppression for the treatment of non-infectious, intermediate, posterior, and panuveitides.[15,21,22,23,24] The MUST Trial enrolled 255 participants (Table 1), and the primary outcome was change in visual acuity from baseline. At 2 and 4.5 years of follow-up, the implant and systemic therapy had similar visual acuity outcomes; both treatments controlled the inflammation in the large majority of participants; the implant had better control of the inflammation but at a cost of higher rates of ocular hypertension (OHT), glaucoma, and cataracts; and both groups had similar rates of systemic side effects, except for a greater use of antibiotics for infections in the systemic group.[21,22,23,24] However, at 7 years of follow-up visual acuity outcomes significantly favored systemic therapy, with greater rates of ocular adverse events in the implant group, but generally similar rates of systemic adverse events in both groups.[15] Furthermore, throughout the 7 years of follow-up, participants on systemic therapy maintained good visual acuity (mean ~20/40).

Clinician-reported causes of visual impairment suggested that patients in the implant group more often had retinal lesions/scars as the cause. These data suggest that systemic therapy has advantages over strictly regional therapies for the long-term management of these more severe, vision-threatening uveitides. In the systemic group, 88% of participants received immunosuppression in addition to oral corticosteroids. Of the 88% of participants using immunosuppression, 85% (75% of the entire cohort) initiated immunosuppression with a single immunosuppressive agent, and 15% (13% of the entire cohort) with a combination of immuno-suppressive agents. The most commonly used single-agent immunosuppressive drugs were mycophenolate 41%, methotrexate 29%, azathioprine 7%, and cyclosporine 6%. The most commonly used combination regimens were mycophenolate and cyclosporine 5%, azathioprine and cyclosporine 3%, and methotrexate and cyclosporine 2%. For each participant the choice of immunosuppressive drug was made by the investigator at the clinical center, based on the patient's needs and the drug's side effect profiles (e.g., methotrexate is avoided in patients with liver disease), but the drugs were used in a standardized fashion following MUST Trial guidelines.[14,21] Adherence to protocol for the use of immunosuppressive drugs was monitored regularly by a Medical Therapy Quality Assurance Committee (MTQAC), thereby assuring their proper and consistent use.

Table 2. Distribution of uveitic diseases in the MUST Trial

Disease	% Participants
Intermediate uveitis (including pars planitis)	27
Undifferentiated anterior and intermediate uveitis	19
Undifferentiated or sarcoid-related panuveitis	17
Multifocal choroiditis with panuveitis	10
Birdshot chorioretinitis	9
Vogt-Koyanagi-Harada disease	6
Undifferentiated retinal vasculitis	5
Behçet disease	3
Multiple sclerosis associated uveitis	1
Other*	3

*Sympathetic ophthalmia, serpiginous choroiditis, and punctate inner choroiditis each 1%

1.9 Rationale for trial

Available data suggest that each of the conventional, non-alkylating-agent, immuno-suppressive drugs is effective in successful corticosteroid-sparing with inflammation control in ~40-55% of patients when used as a single immunosuppressive agent in conjunction with corticosteroids.[28,29,30,31,34] hence, combination therapy often is needed.[16] In June 2016, the United States (US) Food and Drug Administration (FDA) approved adalimumab, a fully-human monoclonal antibody to TNF-α, for the treatment of non-infectious intermediate, posterior, and panuveitides.[37,38] Monoclonal antibody therapies, particularly those against TNF-α, have transformed the management of rheumatic diseases, such as rheumatoid arthritis and ankylosing spondylitis, and largely have supplanted older Disease Modifying Anti-Rheumatic Drugs (DMARDs). Although the relative effectiveness of adalimumab vs. conventional immunosuppression for the treatment of non-infectious intermediate, posterior, and panuveitides is unknown, data from the VISUAL III study suggest that adalimumab may be superior to conventional immunosuppression for corticosteroid sparing while maintaining uveitis control. In VISUAL III uveitis control was maintained in ~75% of participants with prednisone doses $\leq$5 mg/day (Tari S, AbbVie, personal communication, 2016). Minimizing the daily dose of prednisone is important, as there is a cumulative effect of oral corticosteroids on the risk of cardiovascular disease and mortality.[33] Therefore, the ADVISE Research Group proposes to perform a randomized, comparative effectiveness trial of adalimumab vs. immunosuppression with conventional agents for the treatment of non-infectious intermediate, posterior, and panuveitides, the ADlamimumab Vs. conventional ImmunoSupprEssion for uveitis (ADVISE) Trial.

2. Objective and study hypothesis

2.1 Objective and specific aims

The ADVISE Trial is a randomized, parallel-treatment, comparative effectiveness trial, comparing adalimumab to conventional (small molecule) immunosuppression for the treatment of non-infectious, intermediate, posterior, and panuveitides.

The specific aims of the ADVISE Trial are to:

1. Compare the relative effectiveness of adalimumab vs. conventional immunosuppression at controlling ocular inflammation while permitting tapering of prednisone to ≤7.5 mg/day.
2. Compare the relative effectiveness of adalimumab vs. conventional immunosuppression at controlling ocular inflammation while permitting tapering and discontinuation of prednisone.
3. Compare the visual acuity outcomes, rates of ocular complications of uveitis (e.g., macular edema), and drug-related adverse event profiles between the two treatment groups.
4. Compare the quality of life profiles between the two treatment approaches.

2.2 Hypotheses

Based on the preliminary data we hypothesize that adalimumab will be superior to conventional immunosuppression for successful corticosteroid-sparing with no clinically important increase in systemic adverse events.

Primary Hypothesis

Adalimumab will be superior to conventional immunosuppression for corticosteroid sparing, as determined by the proportion achieving the primary outcome, namely inactive uveitis and prednisone ≤7.5 mg/day for 2 visits ≥28 days apart by 6 months of follow-up.

Secondary hypotheses are:

1. Adalimumab will be superior to conventional immunosuppression for corticosteroid-sparing by one year of follow-up as determined by the proportion achieving inactive uveitis at prednisone ≤7.5 mg/day for 2 visits ≥28 days apart within one year of follow-up;
2. Adalimumab will be superior to conventional immunosuppression for maintaining control of inflammation after discontinuation of prednisone for 2 visits ≥28 days apart by one year of follow-up.

3. Design

The ADVISE Trial is a randomized, parallel-treatment, comparative effectiveness trial, comparing adalimumab to conventional (small molecule) immunosuppression for corticosteroid sparing in the treatment of non-infectious, intermediate, posterior, and panuveitides.

3.1 Design elements

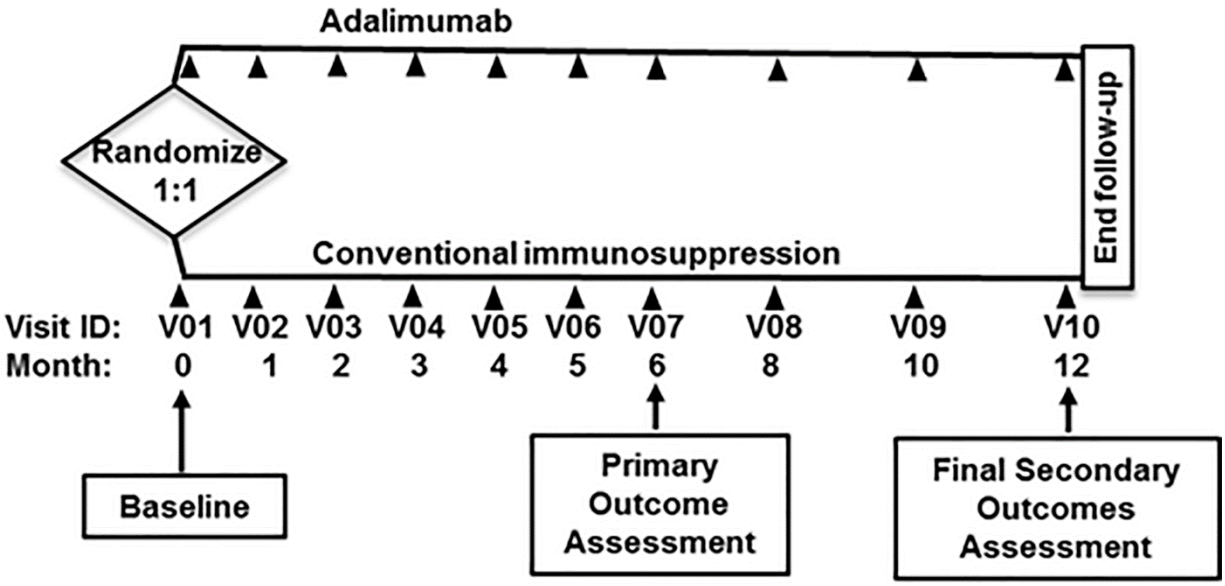
- Randomized, parallel-treatment, controlled comparative effectiveness clinical trial
- Randomization stratified by:
    - Whether patient is receiving zero or one immunosuppressive agent at enrollment
    - Whether the initial dose of prednisone in the trial will be <30 mg/day or ≥ 30 mg/day
- The unit of randomization is the patient
- The unit of analysis for the primary outcome is the patient
- Allocation ratio 1:1
- Multicenter, international
- Fixed sample size = 222 (111 per treatment group)
- Unmasked treatment administration and outcome assessments (participants, study ophthalmologists, visual function examiners, and study coordinators are all unmasked).
- Masked assessment of photographic images and OCT by the RC (graders masked)
    - All patients
        - OCT at baseline, 3, 6, and 12 months
        - Retinal color photographs at baseline, 6 and 12 months
- Disease-specific image or OCT, as applicable, at baseline, 1, 3, 6, and 12 monthsAnniversary close-out at the 12-month visit
- First patient enrolled in September 2019; the end of the trial (completion of follow-up of last patient enrolled) is expected to be February 2023.
- Conducted under IND 132532

3.2 Randomized treatment arms

- Adalimumab
    - 80 mg subcutaneously once as the initial dose
    - 40 mg subcutaneously a week later, then 40 mg subcutaneously every other week thereafter

- Conventional immunosuppression
  The treatment of participants randomized to conventional immunosuppression will depend on whether or not patient is using an immunosuppressive agent at enrollment and, if one is being used, the type of immunosuppressive agent in use.
    - For patients receiving no immunosuppressive agents at the time of enrollment the initial immunosuppressive drug will be an antimetabolite (azathioprine, mycophenolate, or methotrexate)
    - For patients already on one immunosuppressive drug at enrollment, the original drug will be continued at the dose at baseline. Additional treatment will be based on the drug already being received at baseline:
        - Those on an antimetabolite will receive a calcineurin inhibitor
        - Those on a calcineurin inhibitor will receive an antimetabolite

3.3 Trial schematic



3.4 Outcomes

3.4.1 Primary outcome

The primary outcome of the ADVISE Trial will be a corticosteroid-sparing treatment success, defined as inactive uveitis, on prednisone ≤7.5 mg/day for 2 consecutive visits ≥28 days apart within the first 6 months after randomization.[9,16,28,29,30,31,34] The SITE Cohort Study required 2 consecutive visits ≥28 days apart to avoid overestimation of benefits among patients who transiently achieve corticosteroid-sparing, but promptly relapse at the next visit.[28,29,30,31,34] We will use a similar methodology for the same reasons. The prednisone taper schedule used in the ADVISE Trial (see Table 4 in section 4.2.2) is designed to permit clear evaluation of this outcome.

3.4.2 Secondary outcomes

Secondary corticosteroid sparing outcomes

1. The ability to achieve inactive uveitis and prednisone ≤7.5 mg/day for 2 consecutive visits ≥28 days apart within one year of randomization.
2. The ability to achieve inactive uveitis and completely discontinue prednisone for 2 consecutive visits ≥28 days apart within 6 months and one year of randomization.
3. Prednisone exposure (e.g., cumulative prednisone dose and/or mean prednisone dose) in the 2 groups over 1 year with emphasis on the 6-month (primary outcome) and 1-year (end of follow-up) visits.

Other secondary outcomes (assessed at every visit unless otherwise indicated)

4. Best corrected visual acuity measured after a standardized refraction using logarithmic visual acuity charts21[,56,57] over 1 year with emphasis on the 6-month (primary outcome) and 1-year (end of follow-up) visits.
5. Incidence of the following infections over 1 year with emphasis on the 6-month (primary outcome) and 1-year (end of follow-up) visits:
    a. Infections requiring antimicrobial therapy
    b. Tuberculosis (clinical diagnosis of tuberculosis)
    c. Invasive fungal infections
    d. Dermatomal or disseminated herpes zoster

    Diagnosis of these entities will rely on medical record confirmation thereof, but specific testing will not be performed prospectively to ascertain the individual infections, which likely will be unusual.
6. Systemic adverse events, e.g., cytopenias, elevated creatinine, elevated liver enzymes15[,21,22,23,24] over 1 year with emphasis on the 6-month (primary outcome) and 1- year (end of follow-up) visits.
7. Macular edema[58,59,60,73] over 1 year with emphasis on the 6-month (primary outcome) and 1-year (end of follow-up) visits.
8. Quality of life (QoL) data as assessed using the following patient reported outcomes that have been used in prior MUST [61,62,63,64,65,66,67] over 1 year with emphasis on the 6-month (primary outcome) and 1- year (end of follow-up) visits
    a. Health Utility (EuroQoL 5-dimension and visual analog scales)
    b. Generic Health-related Quality of life (SF-36)
    c. Vision-related QoL (the 25-item NEI Visual Function Questionnaire [VFQ])

3.4.3 Disease-specific assessment to permit ascertainment of outcomes pertaining to activity of uveitis

As there is no one uveitis activity measure or simple combination of measures appropriate for all intermediate, posterior, and panuveitides, disease-specific testing/assessment will be used to determine whether the uveitis is active. The specific uveitic diagnosis documented at enrollment (including undifferentiated uveitides by anatomic class) will dictate the disease-specific tests required (Table 2) and the criteria for determining inactive uveitis for that participant (Guidelines for Determining Inactive Uveitis in the ADVISE Manual of Procedures). If the unlikely situation is encountered in which different eyes have different diagnoses, each eye will be assessed using the disease-specific tests indicated for each eye's diagnosis and both eyes must have inactive uveitis for the patient to be counted as inactive for corticosteroid-sparing outcomes. These tests will be performed according to the schedule outlined in Table 2. Some of the assessments are part of the eye examination (e.g., grading of anterior chamber cells and of vitreous haze), but other assessments involving ancillary testing will be done only for selected diseases (e.g., FAF, visual fields, fluorescein angiography) for which the results are relevant to the determination of activity. However, for each participant, the test(s) and methods of assessment will be the same from baseline throughout the duration of the trial, so that a longitudinal assessment of active vs. inactive can be made consistently on an individual participant basis.

Uveitides included in the ADVISE Trial which require specific testing in addition to clinical examination to determine activity/quiescence include:

- Multifocal choroidal/retinal pigment epithelium inflammation including undifferentiated panuveitides (except birdshot chorioretinitis): For most such cases, fundus autofluorescence shows hyper-autofluorescent spots or borders with active disease and hypo-autofluorescent spots with inactive scarring.[55,68,69] Fundus autofluorescence is non-invasive, easily performed, and will be done at each follow-up visit during the trial in patients for which it is indicated.

- Birdshot chorioretinitis: An exception to the utility of autofluorescence for multifocal choroidopathies is birdshot chorioretinitis, where fundus autofluorescence does not correlate with active disease.[55] However, patients with active birdshot choroiditis suffer a progressive loss of visual field. The earliest changes are a loss of peripheral field, not adequately captured on automated perimetry of the central field (e.g., the Humphrey 30-2), but well captured with quantitative Goldmann perimetry[18] or alternative evaluations of the peripheral field (e.g., automated perimetry using both the SITA-fast 30-2 and the peripheral 60 [P60], a suprathreshold screening test of the peripheral field). Therefore, patients with birdshot will undergo one of these two forms of visual field testing at each visit throughout the trial. Quantitative Goldmann visual fields (QGVFs) are performed in a standard fashion and produce visual field scores for I/4 and IV/4 isopters (normal values $\geq$560˚ of total field and $\geq$700˚ of total field, respectively). The inter-test variation in the field is estimated at 16%, so scores within 16% of the previous field will be considered stable.[18] Published data have demonstrated improving QGVF scores with immunosuppression, vs. declining ones without treatment.[16,18] Goldmann perimetry is not universally available; therefore clinical centers without it will use automated perimetry with both evaluation of the central and peripheral field (e.g., Humphrey 30-2 SITA-fast and P60 screening test), in order to address the limitations of Humphrey 30-2 testing alone. As with QGVFs, automated perimetry results within the variability of the test will

be considered "stable" (e.g., ≤3 dB mean deviation for the 30-2 and a change of ≤8 spots missed for the P60, a supra-threshold screening test [Ramulu P, unpublished data, personal communication, 2017]).

- Early stage Vogt-Koyanagi-Harada disease: OCT will be used to determine the resolution of exudative retinal detachments.

- Late stage Vogt-Koyanagi-Harada disease: Fundus autofluorescence will be used to evaluate chorioretinal lesions

- Retinal vasculitis and panuveitis with retinal vasculitis (including undifferentiated panuveitis with retinal vasculitis and panuveitis with retinal vasculitis with systemic disease): Fluorescein angiography will be used to evaluate patients with these conditions. Because resolution of intraretinal hemorrhages can take 3 months after vascular occlusion, the absence of new areas of intraretinal hemorrhage or retinal infarction or non-perfusion in conjunction with no new or increase in areas of retinal vascular staining and leakage will be used as evidence of uveitis control on fluorescein angiography.

Structural complications, such as macular edema, epiretinal membrane formation, and choroidal neovascularization, will be scored separately, as they do not necessarily indicate active inflammation.

In order to obtain consistency of evaluation, the RC will conduct a training session for the study ophthalmologists, emphasizing interpretation of the various modes of imaging and the determination of active vs. inactive disease. In addition, the RC will provide a guidebook with examples of active and inactive disease based on the disease-specific imaging by disease. Real-time central determination of activity by the RC is not feasible logistically, as treatment decisions must be made at the time of the participant's visit, and determination of activity requires examination of the patient as well as the images. However, images taken at the baseline, 1-, 3-, 6-, and 12-month visits, including disease-specific images, will be sent to the RC for interpretation and will be used in quality control evaluations.

The MTQAC will monitor activity assessment with support from the CC from regular screen as well as ad hoc assessments (e.g., site visits). At month, the CC will screen the data stream for discrepancies between the site determination of activity and the corresponding disease-specific criteria for each eye with uveitis. In addition, the CC will compare the RC and clinical evaluation of disease-specific images collected at baseline, 1-, 3-, 6-, and 12-month visits. Discrepancies will be flagged and forwarded to the MTQAC, which will recommend corrective action as needed.

3.5 Eligibility criteria

Inclusion criteria

1. Age 13 years or older
2. Weight 30 kg (66 lbs) or greater
3. Active or recently active (≤ 60 days) non-infectious intermediate, posterior, or panuveitis
4. Prednisone indication meets one of the following:
    a. Active uveitis requiring one of the following
        i. Initiation of prednisone at dose greater than 7.5 mg/day
        ii. Increasing prednisone dose to greater than 7.5 mg/day
        iii. Currently receiving dose greater than 7.5 mg/day
    b. Inactive uveitis on current dose greater 7.5 mg/day
5. Initiation or addition of an immunosuppressive drug (i.e., a conventional immunosuppressive drug or adalimumab) is indicated
6. If currently receiving a conventional immunosuppressive drug, the drug and dose have been stable for at least 30 days
7. Patient able and willing to self-administer subcutaneous injections or have a qualified person available to administer subcutaneous injections
8. If posterior segment disease is present, ability to assess activity in at least one eye with uveitis
9. Visual acuity of light perception or better in at least one eye with uveitis

Exclusion criteria

1. Active tuberculosis or untreated latent tuberculosis (e.g., positive interferon-γ release assay [IGRA] test, such as Quantiferon-gold)
2. Untreated active hepatitis B or C infection
    Active hepatitis B is defined as positive surface antigen; active hepatitis C is defined as positive antibody and positive polymerase chain reaction (PCR)
3. Any of the following baseline lab values
    a. White blood count <3500 cells per microliter
    b. Platelets <100,000 per microliter
    c. Hematocrit <30%
    d. AST or ALT >1.5X upper limit normal value
    e. Serum creatinine >1.1X upper limit normal value
4. Behçet disease
5. Multiple sclerosis or other demyelinating disease
6. For patients with anterior/intermediate or intermediate uveitis without systemic disease, abnormal magnetic resonance imaging (MRI) of the brain consistent with demyelinating disease
7. Severe uncontrolled infection
8. Receipt of a live vaccine within past 30 days

9. Moderate to severe heart failure (NYHA class III/IV)
10. Active malignancy
11. Use of anti-TNF monoclonal antibody therapy within past 60 days
12. History of adalimumab intolerance or ineffectiveness
13. Hypersensitivity to any of the study treatments or their excipients
14. Current treatment with an alkylating agent
15. Current treatment with more than one immunosuppressive drug, not including oral corticosteroids
16. Shorter-acting regional corticosteroids administered within the past 30 days in any eye(s) with uveitis
17. Long-acting ocular corticosteroid implants, i.e., fluocinolone acetonide implant (e.g., Retisert®, Yutiq™, Iluvien®) placed within past 3 years unless uveitis is active in all eye(s) with an implant
18. Systemic disease that is sufficiently active such that it dictates therapy with systemic corticosteroids or immunosuppressive agents at the time of enrollment
19. Immunodeficiency disease for which immunosuppressive therapy would be contraindicated according to best medical judgment
20. Pregnancy or lactation
21. For persons of child-bearing potential or impregnating potential, unwillingness to use appropriate birth control (abstinence, combination barrier and spermicide, hormonal, or intrauterine device) for the next 18 months or plans to become a biological parent within the next 18 months.

    ** In the UK, use of combination barrier and spermicide alone does not meet birth control requirements.*

    † UK female study participants must use highly effective methods of contraception. UK male study participants must use condoms for at least 6 months after the end of study treatment and their female partners of child-bearing potential are recommended to use highly effective contraception for the same duration. In addition, male participants should not donate semen during therapy or for 6 months following discontinuation of study treatment.
22. Medical problems or drug or alcohol dependence problems sufficient to prevent adherence to treatment and study procedures.

3.6 Stratification and randomization

After informed consent is obtained, eligible participants will be stratified based on: 1) whether they are receiving no or one immunosuppressive agents and (2) whether their initial dose of prednisone in the trial will be <30 mg/day or ≥ 30 mg/day. Participants will be randomized 1:1 to adalimumab or conventional immunosuppression by variable-length permuted blocks within these 4 strata. The randomization schedule will be produced in advance by the CC, and the randomization revealed via the ADVISE website after eligibility and stratum are confirmed.

3.7 Data collection schedule

Participants will be followed monthly for 6 months, and every two months thereafter until anniversary study closeout 1 year after randomization. The visit and examination schedule is given in Table 2.

Table 3. Visit and examination schedule

Month	BL*	1	2	3	4	5	6	8	10	12
Visit ID	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**
All patients										
Visual acuity†	X	X	X	X	X	X	X	X	X	X
Medical, ophthalmic, and treatment history	X	X	X	X	X	X	X	X	X	X
Weight and blood pressure	X	X	X	X	X	X	X	X	X	X
Height	X									
Eye examination	X	X	X	X	X	X	X	X	X	X
Optical coherence tomography (OCT)+	X			X			X			X
Retinal color photographs‡	X						X			X
Complete blood count & chemistry panel§	X	X	X	X	X	X	X	X	X	X
Quality of life (EuroQoL, SF-36, NEI-VFQ)	X			X			X			X
Disease-specific tests										
Disease — *Test(s)*										
Birdshot chorioretinitis — Visual field¶	X	X	X	X	X	X	X	X	X	X
Choroiditis (all except birdshot) — FAF‖	X	X	X	X	X	X	X	X	X	X
VKH, early disease — OCT^	X	X	X	X	X	X	X	X	X	X
VKH, late disease — FAF	X	X	X	X	X	X	X	X	X	X
Retinal vasculitis and panuveitis with retinal vasculitis — FA#	X	X	X	X	X	X	X	X	X	X
Tests to identify exclusion characteristics prior to enrollment										
Interferon-γ release assay for tuberculosis (all patients)**	X									
Hepatitis B panel%;hepatitis C antibody (all)	X									
Gadolinium enhanced MRI *for patients with anterior/intermediate or intermediate uveitis without systemic disease only*††	X									
Pregnancy test for women of child bearing potential	X									

* BL = baseline
† Evaluation of best corrected visual acuity after standard refraction
+ OCT centered on fovea
‡ 9-field 50 or 60˚ photographs or wide-field photograph (e.g., Optos)
§ Including creatinine, liver enzymes and serum glucose
¶ Either quantitative Goldmann perimetry or automated perimetry with Humphrey SITA-fast 30-2 and Screening P60 may be used, but once chosen, the visual field testing should be the same for all visit for each individual patient
‖ FAF= fundus autofluorescence
^ OCT centered on fovea & additionally, as needed, OCT centered to capture area with greatest subretinal thickness
Δ VKH = Vogt-Koyangi-Harada
FA = fluorescein angiography
** E.g., Quantiferon Gold
% Including hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody
†† Gadolinium enhanced MRI = magnetic resonance imaging of the brain with a gadolinium based contrast agent (GBCA)

4. Treatment

4.1 Overview

All patients enrolled in the study will be treated with prednisone, along with randomization to one of the two corticosteroid-sparing treatment strategies being studied. Approaches for administration of ancillary treatments that might be required are specified by the protocol.

The decision to taper, escalate, or change therapy will be dictated by the protocol and the study ophthalmologist's evaluation of activity. The study ophthalmologist will manage the medications according to the treatment guidelines described in the protocol and further detailed in the ADVISE Manual of Procedures, accounting for any side effects encountered. The unit of analysis will be the patient, so that active disease in either eye will cause the patient to be classified as having active disease and managed accordingly. In the unlikely event that a patient has different diagnoses in the two eyes, each eye will be assessed as indicated in the ADVISE disease-specific guidelines for determining inactive disease (Manual of Procedures, section 4.2) for the eye's diagnosis, and both eyes must have inactive uveitis for the patient to be counted as inactive for the corticosteroid-sparing outcomes. The presence of complications of the uveitis (e.g., macular edema, epiretinal membranes) will be scored separately and will not be used to determine uveitis activity, following consensus recommendations.[9]

This section provides study treatment guidelines which cover many but not all situations. The guidelines are based on the following basic principles.

1) Initial therapy involves initiating study-specified immunosuppression with initiation of or an increase in prednisone dose if uveitis is active
2) Initiate prednisone taper once activity has been quieted or maximum duration of high-dose prednisone has been reached
3) If uveitis is not controlled after maximum duration of high dose prednisone and maximum advancement of immunosuppression per guidelines, treatment is per best medical judgment.
4) Reactivation during follow-up is treated by
    a. Increasing the dose of prednisone
    b. Advancing immunosuppression if indicated

For situations that are either not covered by these guidelines or are nuanced so that guidelines may not be followed exactly, study ophthalmologists should follow best medical judgement. Additionally, study ophthalmologists may consult members of the Medical Quality Assurance Committee (MTQAC) for guidance.

The time points (e.g., 4 weeks) in the treatment guidelines are targets; variations due to scheduling of study visits are both permitted and expected.

4.2 Systemic corticosteroids

All participants will be treated with prednisone (or an equipotent dose of an alternative corticosteroid if prednisone is clinically inappropriate or unavailable). The maximum allowed prednisone dose is 1 mg/kg/day up to a maximum of 60 mg/day (i.e., 1 mg/kg/day for patients

under 60kg and 60 mg/day for patients at or above 60kg). Table 3 summarizes the initial prednisone dosing for the scenarios described below.

4.2.1 Initial prednisone dose

- *Patients with active uveitis not on prednisone*:
  The initial dose of prednisone is the maximum allowed dose (i.e., 1 mg/kg/day up to a maximum of 60 mg/day) for 2 weeks. Prednisone tapering will be initiated at 2 weeks per section 4.2.2 if the uveitis is controlled. If the study ophthalmologist expects the uveitis to be controlled within 2 weeks, the prednisone tapering may be initiated automatically at 2 weeks without a clinic visit. Should uveitis fail to be controlled after 2 weeks or if the study ophthalmologist did not expect it to be controlled within 2 weeks, the maximum allowed dose will be continued for 2 additional weeks (total of 4 weeks). To avoid complications of systemic corticosteroid therapy, after 4 weeks of prednisone at the maximum allowed dose, prednisone tapering will be initiated per section 4.2.2. If the uveitis is neither controlled nor substantially improved such that it is expected to be inactive by next visit (V03 in 4 weeks), then, immunosuppression will be advanced per section 4.4. Additional advancement of the immunosuppressive treatment will be implemented according to guidelines in section 4.4 until inflammation is controlled or else the best medical judgment point of guidelines is reached**.**

- *Patients already on prednisone with a reactivation of uveitis:*
  The initial dose of prednisone will be increased according to the current dose and the severity of the reactivation. For patients on more than half of the maximum allowed dose (i.e., maximum dose is 1 mg/kg/day up a maximum of 60 mg/day), the dose will be increased to the maximum allowed dose. For patients on less than half of the maximum allowed dose, the dose will be at least doubled but may be increased to any dose between double the current dose and the maximum allowed dose depending upon the severity of the disease. Should uveitis fail to be controlled after 2 weeks of this increased prednisone dose, then an additional 2 weeks of prednisone at the maximum dose, regardless of the initial dose, will be given. If the study ophthalmologist did not expect the uveitis to be controlled within 2 weeks, then the initial prednisone period may be 4 weeks. To avoid complications of systemic corticosteroid therapy, prednisone tapering will be initiated at week 4 per section 4.2.2. At V02 if the uveitis is neither controlled nor substantially improved such that it is expected to be inactive at the next visit (V03 in 4 weeks), then, immunosuppression will be advanced per section 4.4. Additional advancement of the immunosuppressive treatment will be implemented according to the guidelines in section 4.4. until inflammation is controlled or else the best medical judgment point on the immunosuppression guidelines is reached.

- *Patients with recently active but inactive uveitis by enrollment on prednisone >7.5 mg/day*:
  The dose will be held at that level (i.e., the >7.5 mg/day dose patient was on at enrollment) for 4 weeks after initiating the new immunosuppressive agent to enable that agent to have an effect. Prednisone tapering will be initiated at week 4. Should the patient's uveitis become active within those four weeks, they will be managed as described in the preceding bullet.

Table 4. Initial prednisone dosing summary

Status at enrollment	Initial dose (Week 0)	First opportunity to taper*† (Week 2)	Second opportunity to taper (Week 4)
Active, not on prednisone	Maximum allowed dose (1 mg/kg/day if < 60 kg OR 60 mg/day if ≥ 60 kg)	Controlled: Taper Not controlled: Hold at current dose	Controlled: Taper Substantially improved‡: Taper, but not below 7.5 mg/day until inactive.Only advance immuno.suppression if control is not achieved after 4 more weeks. Not controlled: Taper but not below 7.5 mg/day and advance immunosuppression
Reactivated, on prednisone	Current dose ≥ ½ maximum allowed dose§: Increase to maximum allowed dose Current dose < ½ maximum allowed dose: Increase to between double current dose and maximum allowed dose depending on severity	Controlled: Taper Not controlled at maximum dose: Hold at maximum dose for 2 more weeks Not controlled while below maximum dose: Increase to maximum dose for 2 weeks	Controlled: Taper Substantially improved‡: Taper.but not below 7.5 mg/day until inactive. Only advance immunosuppression if control is not achieved after 4 more weeks. Not controlled: Taper,but not below 7.5 mg/day until inactive and advance immunosuppression
Inactive, on prednisone > 7.5 mg/day	Hold at dose at enrollment	Controlled: Continue on same dose Not controlled (i.e. reactivates): Follow instructions for 'Reactivated, on prednisone'	Controlled: Taper Not controlled (i.e. reactivates): Follow instructions for 'Reactivated, on prednisone'

* If the study ophthalmologist does not expect the uveitis to be controlled at 2 weeks, then an initial course of 4 weeks of prednisone can be prescribed. The first assessment of activity would occur at the next scheduled visit (i.e. in 4 weeks).

† If the study ophthalmologist expects the uveitis to be controlled at 2 weeks, then the corticosteroid taper can be automatically initiated at 2 weeks without a clinic visit. The first assessment of activity would occur at the next scheduled visit (i.e. in 4 weeks)

‡ Substantially improved such that uveitis is expected to be controlled by the next visit

§ The maximum allowed dose is 1 mg/kg/day for participants < 60 kg and 60 mg/day for participants ≥ 60 kg

4.2.2 Prednisone tapering schedule and goals

After initially obtaining (or maintaining) quiescence of uveitis with treatment(s) or when the prednisone dose has been used for the maximum duration described in section 4.2.1,

prednisone will be tapered as described in Table 4 below, starting from the dose of corticosteroids they begin tapering from.

- The primary outcome of the trial is a prednisone dose of ≤7.5 mg/day for 2 visits ≥ 28 days apart with inactive uveitis. If a patient is begun on prednisone 60 mg/day, the primary outcome should be reached by 15 weeks of follow-up.

- If a patient achieves the primary outcome, an attempt should be made to taper further and discontinue prednisone. A range of tapering decrements for prednisone doses below 7.5 mg/day is necessary due to the need to taper prednisone more slowly among those already on long-term oral corticosteroid therapy to minimize corticosteroid-withdrawal symptoms but still permit discontinuation by 1 year of follow-up.

- The prednisone dose should not be tapered below 7.5 mg/day if the patient has active uveitis unless required according to best medical judgement.

- If uveitis reactivates during tapering, follow the guidelines for prednisone dosing in the reactivation management guidelines in section 4.5.

Table 5. Prednisone tapering schedule

Dose (mg/day)	Decrement (mg/day)	Interval (decrease every)
60 to 30	10	1 week
30 to 15	5	1 week
15 to 7.5	2.5	1 week
7.5†	*Hold at 7.5 mg/day until two study visits ≥ 4 weeks (28 days) apart have occurred**	
<7.5†	1-2.5	2 weeks

*Note: This may involve maintaining the dose for more than two consecutive study visits if they occur <28 days apart.

† Do not taper below 7.5 mg/day until uveitis is inactive

4.3 Corticosteroid-sparing drugs

Corticosteroid-sparing therapy will be implemented according to strategies assigned by randomization. Patients initially on one immunosuppressive drug will continue it in addition to the randomized treatment. Because of the differences in treatment administration and the use of conventional agents with different treatment administration schedules, treatment administration will not be masked.

4.3.1 Adalimumab treatment group

Adalimumab dosing regimen

- 80 mg subcutaneously once as an initial dose administered as soon as possible after randomization
- 40 mg subcutaneously one week after initial dose and then 40 mg every two weeks until the end of follow-up unless some contraindication to continuation arises

The adalimumab dosing protocol in ADVISE is the FDA approved regimen for treatment of uveitis in adults, i.e., an initial dose of 80 mg followed by 40 mg given every other week starting one week after the initial dose. The FDA approved regimen for treatment of uveitis in pediatric patients (2 years of age or older) ≥30 kg is 40 mg every other week but does not include an initial dose of 80 mg. In ADVISE adolescent patients (13 to <18 year olds) will receive an initial dose of 80 mg. While an initial dose of 80 mg is not FDA approved for treatment of uveitis in adolescents, an initial dose of 80 mg for adolescent/pediatric patients is FDA approved for other conditions, e.g., for adolescent patients ≥30 kg for treatment of hidradenitis suppurativa and for pediatric patients ≥ 40 kg for the treatment of pediatric Crohn's disease.

Management of conventional immunosuppressive agents for patients who are on one at baseline

Patients in the adalimumab treatment group who already are taking a conventional immunosuppressive drug will continue that drug throughout the study (in addition to the adalimumab) unless some contraindication to continuation arises. Those for whom existing immunosuppressive therapy is deemed non-useful should discontinue it before entering the study.

4.3.2 Conventional immunosuppression treatment group

Patients randomized to conventional immunosuppression will be started as soon as possible on a conventional immunosuppressive drug, according to published guidelines,[14] using one of the drugs in Table 5. The study ophthalmologist will select amongst the permissible drugs (methotrexate, mycophenolate or azathioprine for antimetabolites; cyclosporine or tacrolimus for calcineurin inhibitors) taking into account the side effect profile of each drug with respect to the patient's clinical situation. Initial and maximum dosing for antimetabolites and dosing for calcineurin inhibitors will be as outlined in Table 5. Because alkylating agents typically are not used in combination with another immunosuppressive drug, they will not be used in ADVISE, except possibly among those progressing to treatment according to best medical judgment.

Patients receiving no immunosuppressive agents at the time of enrollment

- The initial immunosuppressive drug will be an antimetabolite (azathioprine, mycophenolate, or methotrexate) given at initial dose in Table 5 unless contraindicated

In the MUST Trial antimetabolites were overwhelmingly the initial choice for immunosuppression, and available data suggest similar efficacy (including a randomized trial comparing methotrexate to mycophenolate[70]). Because of the differing side effect profiles,

allowing any of the three drugs will allow more patients to participate than choosing one drug alone but will not compromise the efficacy estimate of conventional immunosuppression, as all 3 drugs have similar corticosteroid-sparing efficacy.

Patients already on one immunosuppressive drug at enrollment will be treated based on the drug being received.

- Patients on an antimetabolite will receive a calcineurin inhibitor as directed in Table 5 unless contraindicated
- Patients on a calcineurin inhibitor will receive an antimetabolite at initial dose in Table 5 unless contraindicated.

Because most patients treated with immunosuppression receive an antimetabolite first, this subgroup largely will consist of the addition of a calcineurin inhibitor. A randomized trial of tacrolimus vs cyclosporine suggested similar efficacy for the two drugs,[35] so either drug can be chosen. This approach mimics conventional clinical care.

Selection of antimetabolite or calcineurin inhibitor

As in the MUST Trial, the choice of antimetabolite and the choice of calcineurin inhibitor in the conventional arm will be made based on the patient's clinical history by the clinician at the clinical center but used in a standard fashion.[21] Initial and maximum dosing for antimetabolites and dosing for calcineurin inhibitors will be as outlined in Table 5 below.

Note: Systemic immunosuppressive drugs other than those mentioned in this section are not permitted as study medications.

Table 6. Conventional immunosuppressive drugs in the ADVISE Trial [14,21]

Class	Generic name	Trade name	Initial dose	Max dose
Antimetabolite	Azathioprine	Imuran	2 mg/kg/day	200 mg/day
	Methotrexate*	Rheumatrex	15 mg/week	25 mg/week
	Mycophenolate	CellCept	1 gm BID	1.5 gm BID
Calcineurin inhibitor	Cyclosporine	Sandimmune	2.5 mg/kg BID	2.5 mg/kg BID
		Neoral	2 mg/kg BID	2 mg/kg BID
	Tacrolimus†	Prograf	1 mg BID	3 mg BID

* Orally or subcutaneously; with folate

† Escalate every 2 to 4 weeks to therapeutic blood level or maximum dose

4.4 Advancement of immunosuppressive treatment

For patients who come in to the study with active uveitis, advancement of immunosuppression is required if uveitis is neither not controlled or substantially improved such that it is expected to be inactive at the next visit four weeks after initiating study-specified medications.

Advancement of immunosuppression is also required if uveitis reactivates during prednisone tapering. See section 4.5 for guidelines for managing uveitis reactivation during prednisone tapering, which requires prednisone increase in addition to advancement of immunosuppression. As noted in section 4.5, if uveitis reactivates after achieving prednisone cessation, the decision of whether to advance immunosuppression should be made according to best medical judgment.

The general hierarchy for advancement of immunosuppression is to (1) maximize the dose of current immunosuppressive drug(s) as applicable; (2) add a new conventional immunosuppressive drug at initial dose and maximize dose as applicable. Patients assigned to conventional immunosuppression may receive two conventional immunosuppressive drugs, an antimetabolite and a calcineurin inhibitor. Patients assigned to adalimumab may receive one conventional immunosuppressive drug. If uveitis cannot be controlled at maximum permitted immunosuppression, patient will be treated per best medical judgment. Additional details are included in the ADVISE Manual of Procedures section 8.4.

4.5 Management of uveitis reactivation

The guidelines for managing uveitis reactivation are summarized in tables 6a. *Reactivation management guidelines*: *Prednisone* and 6b. *Reactivation management guidelines: Immunosuppression*.

The prednisone dose to be used for uveitis reactivation will depend upon whether the reactivation occurs during the prednisone taper or after prednisone cessation. If the uveitis reactivates during the prednisone taper, the dose of prednisone will be at least doubled, up to the maximum allowed dose (1mg/kg/day up to 60 mg/day), depending on the severity of the reactivation per table 6a. If uveitis reactivates after achieving prednisone cessation, prednisone will be reinstated at a dose of at least 10 mg/day up to the maximum allowed dose (i.e., 1 mg/kg/day if < 60 kg or 60 mg/day if ≥ 60 kg), depending on the severity of the reactivation. The study physician will determine whether to advance immunosuppression per best medical judgment.

As adalimumab is FDA-approved at only a single dose, advancement of immunosuppressive therapy will focus on the addition or increase in dose of conventional immunosuppressive agents for both treatment arms. The advancement of conventional immunosuppressive agents will depend upon number and dose(s) of the current medications being used.

For patients on less than the maximum dose of a conventional immunosuppressive agent, it should be increased to the maximum dose in Table 5, as applicable and tolerated. For patients on the maximum dose of a single immunosuppressive drug, a second agent from the other class should be added. For patients on an antimetabolite, a calcineurin inhibitor will be added and vice versa. For patients already on 2 immunosuppressive drugs at maximum doses, best medical judgment will be used, including changing one or both of the currently used immunosuppressive agents.

Although it might be argued that conventional immunosuppressive agents might be used initially at the maximum dose to avoid the dose escalation step, this alternative approach does not mimic clinical practice, whereas the use as outlined in Table 5 does.[14] Furthermore, this approach minimizes the possibility of drug-related side effects, and many patients respond to the initial dose without need for dose escalation.[16,71] For example, among patients who respond to treatment with methotrexate, the majority do so at a dose of 15 mg/week.[71] For patients assigned to conventional immunosuppression requiring changes in the immunosuppressive agent for side effects, an attempt will be made (if possible) to change within class (e.g., a different antimetabolite); if not possible, the alternative class may be used, or if necessary best medical judgment. These guidelines are presented in more detailed outline format in the Manual of Procedures section 8.5.

If uveitis reactivates after achieving prednisone cessation, prednisone will be reinstated at a dose of at least 10 mg/day up to the maximum allowed dose (i.e., 1 mg/kg/day if < 60 kg or 60 mg/day if ≥ 60 kg), depending on the severity of the reactivation. The study physician will determine whether to advance immunosuppression per best medical judgment.

Table 7. Reactivation management guidelines

Table 6a. Reactivation management guidelines: Prednisone			
Scenario	**Action for prednisone dose**	**First opportunity to taper** ***(2 weeks after prednisone increase)****	**Second opportunity to taper** **(4 weeks after prednisone increase)**
Reactivation during prednisone taper	*If current dose ≥ ½ maximum allowed dose, increase to maximum allowed dose* *If current dose < ½ maximum allowed dose, increase to between double current dose and maximum allowed dose depending on severity*	Controlled: Taper Not controlled: If increased dose is not maximum allowed dose, increase to maximum allowed dose	Controlled: Taper Not controlled: Taper but not below 7.5 mg/day until uveitis is inactive
Reactivation after tapered off prednisone	Reinitiate prednisone at dose of at least 10 mg/day up to the maximum allowed dose (i.e., 1 mg/kg/day if < 60 kg or 60 mg/day if ≥ 60 kg), depending on the severity of the reactivation	Controlled: Taper Not controlled: Treat per best medical judgment	Controlled: Taper Not controlled: Treat per best medical judgment

* If the study ophthalmologist does not expect the uveitis to be controlled within 2 weeks of the prednisone increase, then an initial course of 4 weeks of prednisone can be prescribed. The first assessment of activity would occur at the next scheduled visit (i.e. in 4 weeks).

† If the study ophthalmologist expects the uveitis to be controlled within 2 weeks of the prednisone increase, then the corticosteroid taper can be automatically initiated at 2 weeks without a clinic visit. The first assessment of activity would occur at the next scheduled visit (i.e. in 4 weeks)

Table 6b. Reactivation management guidelines: Immunosuppression		
Treatment assignment	**Scenario**	**Immunosuppression management**
Conventional immunosuppression	1 conventional IMT† at initial dose	Increase to maximum dose‡
	1 conventional IMT at maximum dose‡	Add 2nd conventional IMT from alternative class†† at initial dose
	1 conventional IMT at maximum dose‡, 2nd conventional IMT at initial dose	Increase 2nd conventional IMT to maximum dose‡
	2 conventional IMTs at maximum doses‡	Treat per best medical judgment
Adalimumab	Adalimumab only	Add conventional IMT¶
	Adalimumab & conventional IMT initial dose	Increase conventional IMT to maximum dose‡
	Adalimumab & conventional IMT at maximum dose‡	Treat per best medical judgment

† Conventional immunomodulatory therapy (immunosuppressive therapy) drug
‡ Maximum dose = maximum dose of antimetabolite or dose resulting in therapeutic blood level for tacrolimus, up to maximum dose per table in section 8.3.2.1. Note: Cyclosporine has only one dose.
†† If on an antimetabolite, add a calcineurin inhibitor; if on a calcineurin inhibitor, add an antimetabolite.
¶Antimetabolite preferred; either class acceptable

4.6 Monitoring for toxicity of immunosuppressive drugs

Patients will be monitored for potential toxicities of adalimumab or conventional immunosuppressive therapy/therapies using the schedule described in the Trial's follow-up schedule (Table 2), i.e., complete blood count and chemistry panel including creatinine and liver enzymes will be conducted at every study visit and monitoring and prevention strategies will be implemented as detailed in Table 7. *Potential Risks of Therapy*. As applicable, additional monitoring studies should be carried out per routine care.[14] When potential toxicities are encountered, modification of therapy, including dose reduction or discontinuation as clinically appropriate, should be done along the lines indicated in published guidelines.[14]

4.7 Discontinuation of treatment within the assigned treatment arm

4.7.1 Discontinuation for toxicity

As applicable, when toxicity cannot be managed through modification of treatment regimen, assigned treatment may be discontinued and participant managed according to best medical judgment.

4.7.2 Discontinuation for pregnancy

If a participant becomes pregnant, methotrexate and mycophenolate must be discontinued as methotrexate is known to increase the risk of spontaneous abortion and malformations and mycophenolate is known to increase the risk of malformations. Consideration should be given to discontinuation of azathioprine, cyclosporine, tacrolimus, and adalimumab. Participants should be managed according to best medical judgment.[72]

4.8 Ancillary therapy

4.8.1 Regional corticosteroid Injections

The MUST Trial demonstrated that the majority of patients with uveitic macular edema require supplemental regional corticosteroid injections (either periocular or intravitreal) to improve the macular edema, but that they typically need only one or two injections.[73] Therefore, participants in the ADVISE Trial with uveitic macular edema will be permitted a regional corticosteroid injection within the first 2 months, if needed, and a second injection during months 6 to 8 (if needed) for persistent macular edema (to meet patients' clinical needs without contaminating key outcomes). Acceptable regional injections are: 1) periocular triamcinolone acetonide 40 mg, 2) intravitreal triamcinolone acetonide 4 mg (Triesence® [Alcon Laboratories, Inc., Fort Worth, TX] preferred if available due to its being preservative free for intravitreal use).or 3) the dexamethasone intravitreal pellet (Ozurdex ®, Allergan, Inc., Irvine, CA).[5474] **If a participant is given an injection during the first 2 months of the trial, the dose of prednisone should not go below 7.5 mg/day (or if already <7.5 mg/day, should not be tapered further) until 3 months after the injection, as the primary outcome only can be ascertained 3 months after an injection**. Allowing the limited use of regional corticosteroid injections for uveitic macular edema is necessary for proper clinical care, and the restrictions on their use will permit evaluation of the trial's outcomes.

4.8.2 Topical corticosteroids

- Adjunctive use of high doses of topical corticosteroids (up to one drop hourly of prednisolone acetate 1%, prednisolone sodium phosphate 1% or loteprednol etabonate 0.5%, or one drop six times daily of difluprednate 0.05%) is permitted for up to two weeks after anterior chamber uveitic activity is first observed.
- Upon quiescence of the anterior chamber inflammation, topical corticosteroids should be tapered
- Maintenance therapy of not more than prednisolone acetate 1% or loteprednol 0.5% three times daily or difluprednate 0.05% one drop daily is permitted.
- Failure to control anterior chamber inflammation using this approach should be addressed with systemic corticosteroids and immunosuppression.
- Discontinuation of such therapy, when feasible, is encouraged

4.8.3 Non-corticosteroid ophthalmic medications

These may be used according to best medical judgment.

4.8.4 Systemic medications other than corticosteroids and immunosuppressive drugs

These may be used according to best medical judgment.

4.8.5 Treatment monitoring

Treatment will be monitored for consistency with the treatment guideline by a member of the MTQAC,[21] MTQAC will monitor treatment patterns as revealed in the data stream, site visits, etc., and investigate inconsistencies with treatment guidelines, providing remediation as appropriate.

5. Study treatment procurement

Adalimumab will be donated by AbbVie (Chicago, IL); distribution to clinical centers is described in the manual of procedures. Prednisone and conventional immunosuppressive study treatments are not provided by the study and will be obtained per standard care.

6. Possible side effects and complications of study treatments

Although there are potential risks associated with systemic corticosteroids and immunosuppression, they typically are reversible with dose reduction or discontinuation of the drug. The MUST Trial and Follow-up Study demonstrated that there was essentially no increased risk of these events compared to treatment with a strictly regional therapy, the fluocinolone acetonide implant, with the one exception of a greater use of antibiotics among participants receiving systemic therapy.[15,22,23,24] Hence, with appropriate use, these risks can be minimized. Thus, the risks associated with participation in the ADVISE Trial are expected not to be greater than those associated with clinical care for patients with these uveitides. Possible side effects of the randomly assigned study treatments and of corticosteroids are summarized in Table 7.

Patients in ADVISE Trial will receive oral corticosteroids for treatment of uveitis, as they would in clinical care. The potential side effects of oral corticosteroids include water retention, weight gain, headache, muscle weakness, loss of muscle mass, face puffiness, growth of facial hair, easy bruising, acne, rounding of the upper back, irregular menstrual periods, insomnia, mood swings, increased energy, personality change, hypertension, hyperglycemia, and hypercholesterolemia. Oral corticosteroid therapy may lower resistance to infections, make infections harder to treat, slow wound healing, and increase the risk of osteoporosis. Aseptic necrosis of bone is a rare but serious complication. For persons already at risk of congestive heart failure, corticosteroids can increase the risk. Side effects occur more often with longer treatment and with higher doses, and typically resolve when dosage is lowered or treatment is discontinued. As noted previously, serious complications such as these are very rare, particularly when appropriate management is used, as was done in the MUST Trial, including aggressive tapering of prednisone to a dose $\leq$7.5 mg/day[15,22,23,24] In the MUST Trial and Follow-up Study, there generally was no significant increase is systemic side effects with systemic therapy through 7 years of follow-up.[15,22,23,24] Ocular side effects seen in the eyes of patients with uveitis treated with systemic corticosteroids include the need for cataract surgery at ~6%/year, ocular hypertension at 3%/year, and glaucoma at 1.3%/year.[15] Typically, these side effects are lower than with alternatively local therapies, as was demonstrated in the MUST Trial.[15,22,23,24]

In addition to corticosteroids, patients in the ADVISE Trial will receive immunosuppressive agents, either conventional (small molecule) drugs or the biologic adalimumab. For many of these diseases, immunosuppression has been shown to produce superior outcomes.[15,17,18,19,20] The eligibility criteria select patients for whom immunosuppression is indicated, so that patientsare not expected to experience any greater risk than would be seen with clinical care. Conventional immunosuppressive agents with activity against uveitis that will be used in ADVISE are the antimetabolites, azathioprine (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF); and the calcineurin (or T cell) inhibitors, cyclosporine (CSA) and tacrolimus (TAC).[14] Because of the potential increased risk of cancer associated with alkylating agent use, and because they are not used in conjunction with other immunosuppressive drugs, cyclophosphamide and chlorambucil will not be used in the trial,[43,44,45,46,47] unless the patient suffers sufficient relapses that (s)he is treated with best medical judgment. Each of these agents is associated with its own spectrum of potential systemic side effects. Side effects associated with these medications that are medically important and expected to occur with detectable frequency during the trial are described below.[14] The ADVISE Trial will conduct surveillance for these potential risks in a protocol-directed manner that approximates medical care (see Table 7). However, the side effects mentioned below did not occur with higher frequency in the systemic therapy group of the MUST Trial than in the strictly local therapy implant group.[15,22,24]

Bone marrow suppression: a) Reversible neutropenia – which may occur with AZA, MTX, MMF, TAC – will be evaluated over time as the cumulative proportion having a total white blood cell (WBC) count 2500 cells/μL or fewer, which still is above the level for an increased risk of infection, and is a common indication for interruption of therapy. Change in WBC count from baseline and use of granulocyte stimulatory factors also will be noted; b) Reversible thrombocytopenia – which may occur with AZA, MTX, MMF, TAC – will be evaluated over time as the cumulative proportion having a platelet count 100,000/μL or fewer, which is a common indication for suspension of therapy. Hemorrhagic events and requirement for platelet transfusion or other treatments for thrombocytopenia also will be noted; c) Reversible anemia – which may occur with AZA, MTX, MMF, CSA, TAC – will be evaluated over time as the cumulative proportion having a hemoglobin level $\leq$10 g/dL, a level often considered clinically meaningful. Use of transfusions and of erythropoietin also will be noted; and the occurrence of myelodysplasia will be noted if confirmed in medical records.

Reversible hepatotoxicity -- which may occur with AZA, MTX, MMF, CSA, and TAC -- will be evaluated over time as the cumulative proportion with any of the following, verified in medical records: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than two times the upper range of normal confirmed by repeat testing; OR discontinuation of an immunosuppressive agent due to hepatotoxicity. Cases of persistent elevation of AST and/or ALT after discontinuation of the offending agent will be noted.

Reversible nephrotoxicity -- which may occur with CSA and TAC -- will be evaluated over time as the cumulative proportion with: serum creatinine level elevated 30% above baseline or to a level of 1.5 mg/dL or higher OR discontinuation of an immunosuppressive drug for renal toxicity. Persistent renal insufficiency will be noted.

Pregnancy risks: MTX and MMF are associated with increased risk of first trimester pregnancy loss and congenital malformations; women of child bearing potential and men taking MTX are advised to use adequate birth control during the trial, and especially if taking these medications.

Infection: even without an increased risk of leukopenia among patients in the (unmasked) MUST Trial on systemic therapy, there was an increased use of antibiotics for infection.[15,22,23,24] However, there were no long-term sequelae from these infections, and no increase in the risk of hospitalization for infection.[15] Patients will be queried about infections at every visit, and medical records reviewed as necessary, to monitor for infections. Hospitalization data also will be collected. In non-uveitis use (e.g., transplants) some immunosuppressive regimens may increase the risk of severe opportunistic infections (e.g., progressive multifocal leukoencephalopathy), which can have serious consequences, including death. Although there were no such events in the MUST Trial, because of their rare nature, their possible occurrence in the ADVISE Trial or routine clinical practice using these drugs cannot be excluded.

Additional recognized potential complications of potent immunosuppressive therapy will be deemed to be present when diagnosis is confirmed by medical records. These conditions specifically will include a diagnosis of any of the following conditions (if not present at baseline): a) liver cirrhosis; b) interstitial pneumonitis; c) possibly malignancy (drug-specific); d) end-stage renal insufficiency.

In addition to these small molecule immunosuppressive agents, the anti-TNF-α biologic agent adalimumab will be used.[33] The most common adverse reaction of adalimumab is redness, itching, pain, or swelling at the injection site, reported in 20% of patients. Other less common adverse events include: increased risk of infections, particularly tuberculosis, fungal infections, and herpes zoster. Patents randomized to adalimumab will be instructed not to get any live

vaccines. Other uncommon potential adverse effects include gastrointestinal symptoms such as nausea, vomiting, abdominal pain, or diarrhea; reversible bone marrow suppression; and reversible hepatotoxicity. Other rare adverse events include: development of anti-adalimumab antibodies and a lupus erythematosus-like syndrome, and a worsening of demyelinating disease, such as multiple sclerosis. All patients enrolled in the ADVISE Trial will have tuberculosis testing with either an interferon-γ release assay test, such as the Quantiferon-gold test and testing for active hepatitis B or C infection[75,76] prior to enrollment. Active tuberculosis and untreated latent tuberculosis and untreated active hepatitis B or C infection are exclusions to participation. Because of the increased risk of multiple sclerosis in patients with pars planitis and undifferentiated intermediate uveitis,[11,12] all potential participants with these two diseases will undergo neuro-imaging with a gadolinium enhanced MRI scan and patients with evidence of possible demyelination are excluded from the trial.

Use of the following medications are prohibited during the trial for safety reasons

- Live vaccines
- Substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life threatening events, e.g. bosentan, dabigatran etexilate and aliskiren.
- Products containing Hypericum perforatum (St John´s Wort) to avoid risk of interaction with tacrolimus that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus

Table 8. Potential risks of therapy

Treatment	Group affected	Systemic	Monitoring & Prevention Strategy
Corticosteroids	Both groups	Hyperglycemia	History; CMP testing
		Hypertension	History; BP measurement
		Osteoporosis	Routine monitoring/ data collection
		Hyperlipidemia	Routine monitoring/ data collection
		Infection	Routine monitoring/ data collection
		Cardiovascular Disease	Routine monitoring/ data collection; Monitor risk factors (per above)
		Cataract	Slit lamp examination/Eye Exam
		Intraocular Pressure Elevation and Glaucoma	Eye Examination
Adalimumab	Adalimumab	Infection	Pre-randomization tuberculosis and hepatitis B and C testing; Routine monitoring/ data collection. Live vaccines should not be given.
		Worsening of multiple sclerosis	MRI of patients with intermediate uveitis at BL; Routine monitoring/ data collection
		Injection Site Reaction*	Routine monitoring/ data collection
		Bone marrow toxicity*	CBC testing
		Hepatotoxicity*	CMP testing, pre-treatment Hepatitis panel
Methotrexate	Conventional	Bone marrow toxicity*	CBC testing
		Hepatotoxicity*	CMP testing, pre-treatment Hepatitis panel
		GI intolerance*	History/Routine monitoring
		Teratogenicity/ Miscarriage	Birth control use for women and men
		Alopecia*	Routine monitoring/ data collection
Mycophenolate	Conventional	Bone marrow toxicity*	CBC testing
		Hepatotoxicity*	CMP testing, pre-treatment Hepatitis panel
		GI intolerance*	History/Routine monitoring
		Teratogenicity	Birth control use
		Possibly PML (disputed)	History/Routine monitoring

Treatment	Group affected	Systemic	Monitoring & Prevention Strategy
Azathioprine	Conventional	Bone marrow toxicity*	CBC testing
		Hepatotoxicity*	CMP testing, pre-treatment Hepatitis panel
		GI intolerance*	History/Routine monitoring
Cyclosporine	Conventional	Hypertension*	History; BP measurement
		Renal insufficiency*	CMP testing
		Tremor/paresthesia*	History/Routine monitoring
		Hirsutism*	History/Routine monitoring
		Gingival hyperplasia*	History/Routine monitoring
Tacrolimus	Conventional	Hypertension*	History; BP measurement
		Renal insufficiency*	CMP testing
		Tremor/paresthesia*	History/Routine monitoring
		Hyperglycemia*	History; CMP testing
		Interactions with products containing Hypericum perforatum	Products containing Hypericum perforatum (St John´s Wort).may not used during the study

*Usually reversible with dose adjustment or cessation of therapy

CMP=complete metabolic panel; BP=blood pressure; CBC=complete blood count

7. Safety reporting of adverse events

7.1 Adverse events

Adverse events (AEs) and complications of study treatment will be submitted to the CC. As described in section 7.2, all serious adverse events (SAEs) will require expedited reporting to the CC for immediate review by the CC Safety Officer who will determine any further actions required including whether the event requires expedited review by the Data and Safety Monitoring Committee (DSMC) Safety Officer. The CC and DSMC Safety Officers will make recommendations to the DSMC as to any actions that may be needed.

7.2 Serious adverse events

An SAE is an adverse event that results in one of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or congenital anomaly/birth defect. Also, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention (treatment) to prevent any of the outcomes previously listed in this definition.

Clinical centers will report all SAEs to the CC expeditiously regardless of the relationship to study treatment. When an investigator or clinical center staff member becomes aware of an SAE, it will be reported to the CC within 72 hours (within 24 hours for UK clinics only*) with follow up reporting until the event is terminated. The SAE report will include an assessment by the clinical investigator at the managing clinical center as to the likelihood whether the event is related to treatment. Upon receipt at the CC, the SAE report will be sent to the CC Safety Officer for immediate review and determination as to whether the event meets the criteria for a safety report and whether expedited review by the DSMC Safety Officer is warranted.

All serious and unexpected events possibly related to study treatment will be reported as safety reports to the NEI project officer, the pharmaceutical supplier (where appropriate), applicable regulatory agencies (.e.g., FDA and Health Canada), and all clinical centers in accordance with applicable regulations. The CC and clinical centers will submit all safety reports as expedited reports to their Institutional Review Boards (IRBs). Reports of SAEs not deemed to be unexpected will be submitted to the CC's IRB, to the IRB of the clinical center in which the event was reported, as well as to any other study center IRBs which require such reports.

*For compliance with the CT3 directive (2011/C 172/01) (Section 4.3.1): "Communication from the European Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinicaltrials on medicinal products for human use

8. Sample size and statistical methods

8.1 Hypotheses

The primary hypothesis is that adalimumab will be superior to conventional immunosuppression for corticosteroid sparing, as determined by the proportion of participants that achieve the primary outcome, namely inactive uveitis and prednisone ≤7.5 mg/day for 2 visits ≥28 days apart by 6 months of follow-up. The 6-month time frame was chosen to allow sufficient time to observe the primary outcome regardless of the patient's prednisone dose at randomization and is likely to be more robust to imbalances.

Secondary hypothesis are that adalimumab will be superior to conventional immunosuppression for:

- Corticosteroid sparing (inactive uveitis and prednisone ≤7.5 mg/day for 2 visits ≥28 days) apart by one year of follow-up
- Prednisone discontinuation (inactive uveitis for 2 visits ≥28 days after discontinuation of prednisone) by one year.

Furthermore, we hypothesize that these benefits will be accomplished with no increase in ocular or systemic adverse events (other than injection site reactions) with adalimumab, and that both approaches will produce similarly visual acuity and incidences of uveitic complications.

8.2 Sample size and power calculations

Sample size is calculated for the primary comparison of corticosteroid-sparing treatment success (inactive uveitis and prednisone <7.5 mg/day for 2 consecutive visits >28 days apart) at 6 months. Based on the preliminary data from the VISUAL III Study, we estimate that adalimumab will be successful in achieving the primary outcome in 75% of patients across all strata. The success of conventional small molecule immunosuppression varies according to the type and number of treatments. Based upon the Mount Sinai and MUST Trial data, we estimate that 75% of the participants will be in the stratum of no prior immunosuppression and 25% will be on one immunosuppressive agent at enrollment.[16] Based on the SITE data, the estimated success rate for antimetabolites is 55% and for calcineurin inhibitors 40%.[28,29,30,31] Patients in the no immunosuppression stratum will receive antimetabolites, whereas those in the one immunosuppression stratum will largely receive calcineurin inhibitors. Therefore, success rates of 55% and 40% are estimated for the no and one immunosuppressive agent strata, respectively. Based on the estimated stratum proportions and corresponding success rates, the overall conventional immunosuppression success rate is estimated to be 51%. In the MUST Trial, the loss to follow-up was 6% at 2 years. In order to be conservative, we will assume a 10% loss to follow-up in each group and that all individuals were lost prior to observing a result. Under these assumptions, a sample size of 222 (111 participants per treatment group) provides 90% power to detect significant differences between the 2 groups if the underlying true proportions are 51% vs. 75% (46.1% vs. 67.5%, respectively, after adjusting for the loss to follow-up), assuming a two-sided type I error of 0.05. VISUAL I and II, while not appropriate for estimation of corticosteroid-sparing due to a rapid taper, do provide some estimates of the ability to discontinue prednisone, which can be estimated as 50%. Based upon data from Mount Sinai and the MUST Trial, estimates of the discontinuation rates for standard immunotherapy range between 11%-35%. A sample size of 222 provides 80% power to detect an increase in the secondary outcome of discontinuing prednisone while controlling the uveitis

by 1 year from 30% to 50% (estimated from VISUAL I and II data), assuming a two-sided type I error of 0.05.

8.3 Statistical analysis plan

A detailed description of the statistical principles and analyses is provided in the Statistical Analysis Plan. The primary analyses will be based upon assigned treatment and will include all available data, following the principles of intention to treat, with additional sensitivity analyses based upon treatment received. The primary analyses will include adjustment for randomization strata (immunotherapy use and prednisone dose). Additional analyses that are unadjusted or are adjusted for potential confounders including but not limited to age, gender, race, and uveitis class (e.g., intermediate, posterior, panuveitis) will also be performed as secondary analyses Robust standard errors will be computed using statistical program-based approaches when available and a bootstrap with the individual as the sampling unit when a pre-programmed approach is not available.

The primary goal of the trial is to establish whether adalimumab is superior to conventional immunosuppression for corticosteroid-sparing in the treatment of individuals with intermediate, posterior, or pannuveitis. The analysis will focus on the cumulative proportion with a corticosteroid sparing success. Once a success has been achieved, then it will remain fixed for that individual thereafter. A more standard time to event analysis, which allows for censoring due to loss to follow-up, was considered. However, because the time required to taper prednisone to < 7.5 mg/day depends substantially on the initial/enrollment dose, small imbalances at baseline could influence greatly such analyses despite stratification. Therefore, time to event analyses will be used as sensitivity analyses. The 6-month time frame was chosen to allow sufficient time to observe the primary outcome regardless of the participant's prednisone dose at randomization and is likely to be more robust to imbalances. Multiple imputation will be used to address missing data due to missed interim visits and loss to follow-up.

Since a minimum of two follow-up visits must occur prior to achieving a corticosteroid success and prednisone must be tapered, the first outcome evaluation will occur at 2 months (V03) and will continue for every visit thereafter. Modeling will focus upon the period between 6 months and 1 year due to the potential for imbalances in the tapering patterns described above. Generalized estimating equations (GEE) will be used to fit logistic regression models comparing the two treatment groups over time while accounting for the correlation between replicate measurements. A saturated mean structure including visits starting at 6 months (V07-V10), treatment, and visit by treatment interaction terms plus the two stratification variables (baseline immunotherapy and initial prednisone dose) will be used. The 6-month visit by treatment interaction will be used to assess the primary outcome. An unstructured correlation matrix will be used to model the within-individual repeated measurements. Alternate correlation structures (e.g., exchangeable) will be explored if the unstructured covariance matrix is unstable. This model estimates the relative odds of corticosteroid-sparing for adalimumab vs conventional immunosuppression. A standardized estimator, which allows for covariate adjustment, will be used to compare the absolute (as opposed to relative) difference in proportions at each timepoint based upon the logistic model described above and a bootstrap estimate of the 95% confidence intervals. This estimator has the advantage of providing a consistent estimate even if the means model is mis-specified.[77,78] Analyses of the secondary hypotheses will follow the same data management and analysis structure.

9. Regulatory and ethical issues

9.1 Recruitment and informed consent procedures

Patients will be recruited at each clinical center by clinicians who will present the opportunity to participate in the trial, discussing the potential risks and benefits in the patient's particular circumstances. Patients choosing to participate will give written consent. Adolescents and their parent or legal guardian will give written assent or consent according to the guidelines of the clinic's governing IRB.

A detailed, IRB-approved, informed consent document will be provided, and the patient will be provided ample opportunity to review it. Study staff will make themselves available to answer any questions potential participants will have. Anonymous data will be collected regarding non-participants in compliance with CONSORT guidelines, so as to permit those reviewing the results of the study to know how many people did not enroll, and why they did not enroll. Clinical center consent forms are based on prototypes prepared by the CC and approved by the CC's IRB, the Johns Hopkins University Bloomberg School of Public Health IRB Office. The prototype consent, written at an approximately 9th grade reading level as rated by word processing software, is distributed to the clinical centers. Although clinics may rearrange information and modify language of the prototype to conform to local IRB templates and guidelines, deletion of information considered by study leadership to be essential to an informed consent process is not permitted. For the ADVISE Trial, as in the MUST Trial, consents will be approved by all governing IRBs and will be required to include these key elements: 1) the purpose of the study; 2) selection of participants; 3) study visit schedule and study procedures; 4) involved treatments; 5) risks associated with study procedures, uveitis, and uveitis treatments; 6) potential benefits of participation; 7) the voluntary nature of participation; 8) assurances that the patient's treatment will not suffer if he or she declines enrollment or enrolls, but subsequently withdraws consent; 9) the names and whereabouts of contact persons; 10) explanation of costs for which the patient or patient's insurer will be responsible and costs which will be paid for by the study (i.e., procedures and treatments that are required for the patient's clinical care will be charged to patient's insurance and patient is responsible for any co-pays; procedures done for study purposes only will be paid for by the study) 11) steps taken to protect patient confidentiality; 12) payments to assist with the costs of participation (e.g., parking, transportation); 13) that short-term care will be arranged if the patient is injured as a result of participation in the study but that there is no plan for NIH or the institution to pay for such care; and 14) all other elements required by applicable government regulations. At the beginning of each study, as part of clinic certification, the CC reviews each clinic's IRB approved consent to assure that each local consent statement retained the required information.

Over the course of the study as modifications to the consent are required, the CC revises the prototype consent and, after Johns Hopkins University Bloomberg School of Public Health IRB Office approval has been obtained, distributes the revised prototype to clinics with instructions for revising their local consents. The CC tracks clinics' IRB approvals for consent revisions, maintains an archive of clinics' IRB-approved consents, and monitors IRB approvals to ensure approvals remain current. Enrollment or conduct of study follow-up, absent the necessary IRB approvals, is not permitted. Site visits to clinics include a review of IRB approvals, of correspondence with the local IRB, and of consent documents signed and dated by individual patients and witnessed by clinic personnel.

9.2 IRB/Protection of human subjects

This protocol will be submitted to the IRB of participating centers for review and approval. Clinics may not recruit patients into the ADVISE Trial prior to approval of this protocol by their governing IRB. All ADVISE Trial patients must sign a consent statement and medical record release form as well as HIPAA – complaint privacy practices acknowledgment prior to participation in the study.

Surveillance of uveitis and treatment complications is conducted throughout the study; any such complications encountered are managed by the best medical judgment of the treating ophthalmologist. These events are recorded on study data forms and are submitted to the CC. Summaries of these data are reviewed by the DSMC at each meeting. Important, serious, or unusual adverse events require expedited reporting to the CC and are reviewed by the CC Safety Officer, who makes the determination as to whether the event meets the criteria for a safety report and whether expedited review by DSMC Safety Officer is warranted. The CC Safety Officer follows all serious adverse events through resolution. All serious and unexpected events possibly related to uveitis treatment will be reported as safety reports to the NEI project officer, the FDA, the pharmaceutical supplier (where appropriate), and all clinical centers in accordance with FDA regulations. The CC and clinical centers will submit all safety reports as expedited reports to their IRBs. Reports of serious events not deemed to be unexpected will be submitted to the CC IRB, to the IRB of the clinical center in which the event was reported, as well as to any other study center IRBs, which require such reports.

Confidentiality of patient data will be maintained in accordance with legal regulations. Protected health information (PHI) not be transmitted to the CO, CC, RC, or to other ADVISE sites. PHI collected for study purposes, possibly including name, social security number, address, and other such personal data will be kept solely at the clinical center where the patient receives her/his clinical care and will be kept in a secure location. A dataset limited so as to contain a minimal amount of protected health information–that required to make the data useful for accomplishing the purposes of the ADVISE Trial–may be disclosed, as needed, to collaborating ADVISE sites and the NEI, as will be stated on a study privacy acknowledgment form signed by the participant at the time of enrollment. Also included in the privacy acknowledgment is the statement that representatives of NEI, the Institutional Review Boards, and CC may see identifying information while reviewing study records. This privacy acknowledgment will be designed to conform with specifications of HIPAA regulations, and any other relevant regulations, as approved by the local governing authorities invested with oversight of HIPAA regulations at each participating site. Clinically relevant information from the study may be placed in the patient's medical record. Release of protected health information to any other persons or organizations will require additional written consent of the patient affected, except as required by law.

9.3 Data and Safety Monitoring Committee

Trial monitoring will be conducted by an independent DSMC, appointed as advisory to the Executive Committee (EC) and the NEI. The DSMC is responsible for review of efficacy and safety data, policy and ethical issues, and study performance. The DSMC is composed of two ophthalmologists, one rheumatologist, two biostatisticians, and an ethicist; other members may be added as deemed appropriate by the ADVISE Executive Committee (EC) and the NEI. One of the physician members of the DSMC, will serve as the DSMC Medical Safety Officer to review individual events or summary safety data between DSMC meetings, as deemed necessary by the CC Medical Safety Officer. Treatment effects monitoring, including formal interim analyses, will be performed by the CC and presented to the DSMC. The frequency and

type of analyses and evaluation is determined by the ADVISE Trial EC, NEI, and DSMC, with a minimum of at least two meets, typically one face-to-face and one conference phone call meeting, of the DSMC per year. The policies and procedures for the DSMC analyses and deliberations are modeled on those we have used for other NEI-sponsored trials. The primary focus of the DSMC analyses will be on the comparison of the treatment groups with respect to safety and efficacy measures, which will include, but not be limited to, successful corticosteroid sparing, measures of visual acuity, quality of life, uveitis activity, uveitis complications, ocular and systemic adverse events, etc. Presentation of the statistical methods that are used will be made by selected members of the Statistical Advisory Committee to the DSMC. The DSMC will not be masked. The DSMC may make recommendations to modify the protocol or to terminate the trial if there is early evidence of benefit or harm associated with one of the treatments. Summaries of DSMC reviews and recommendations are submitted to the CC and to each clinical center's IRB for review.

Performance monitoring will include comparisons of enrollment, baseline variables, protocol deviations, and missing data between clinics. Clinic performance data will be presented at DSMC, Steering Committee, and Research Group meetings.

10. Study implementation

10.1 Study organization

The ADVISE Research Group (RG) consists of participating clinical centers and three resource centers: the CO, the CC, and the RC). The resource centers are funded via U10 cooperative agreements and the clinical centers via subcontracts with the CC. The responsibilities of the clinical and resource centers and the committee structure for the ADVISE Research Group are detailed in the ADVISE Manual of Procedures.

10.1.1 Characteristics of target population and recruitment strategies

The population of interest is that to which results of the trial will be generalized. Recognizing that ethical considerations limit participation to those who agree to become clinical trial subjects, we aim to recruit a study population reasonably similar to the population of interest, which is the group of patients for whom immunosuppressive drugs would be prescribed as a treatment for intermediate, posterior and panuveitis. This objective will be accomplished by recruiting subjects from clinical practices that administer immunosuppressive therapy for eye diseases on a frequent basis. The distribution of uveitis disease types in the recruited study population for ADVISE is likely to resemble the distribution of uveitis disease types for the population recruited for the MUST Trial which is provided in Table 1.

10.2 Quality assurance

10.2.1 Medical Therapy Quality Assurance Committee

The MTQAC is a committee of 3 experienced uveitis experts, involved in management of the ADVISE Trial, but not in managing patients enrolled in the trial. The primary role of the MTQAC is to ensure adherence to the assessment of activity and treatment guidelines. Additional details of each type of monitoring are provided below. During the design phase, members of the MTQAC will work with the CC to design forms to capture the details required to assess adherence, to develop rules to flag potential non-adherence, and to determine the format and data to be included in the reports that will be transmitted from the CC to the MTQAC for review.

In addition, they will lead the training of study ophthalmologists on the treatment protocol and serve as a resource for treatment-related questions throughout the trial.

At the start of the trial, there will be intensive scrutiny. Once a site has been certified and is open for enrollment, all available data on activity and treatment from the first two participants enrolled at that site will be reviewed by a member of the MTQAC. The evaluations described below will be included as part of the intensive monitoring plan. Thereafter, a combination of regularly scheduled and ad hoc reviews (e.g., triggered by issues identified during site visits, monthly review of the study data, or other mechanisms) will be performed throughout the course of the study.

A member of the MTQAC will review each report provided by the CC and determine whether corrective action (e.g., retraining, site visit) is required. The entire MTQAC will hold quarterly conference calls to discuss patterns of deviations and to formulate recommendations regarding the need for additional training, monitoring or changes to the protocol. Additional ad hoc meetings will be scheduled as necessary. MTQAC members will be included in site visits to clinics of concern, and the Study Chair will engage centers resistant or repeatedly inconsistent with activity assessment accuracy and/or protocol treatment implementation.

10.2.2 Visual Function Quality Assurance Committee

The Visual Function Quality Assurance Committee (VFQAC) monitors and certifies visual acuity and visual field examiners. It is regularly present at site visits to the individual clinical centers and conducts training and certification of coordinators and other appropriate personnel at RG meetings. In the ADVISE Trial, the visual function protocol and the VFQAC activities will conducted in the same manner we have used for other NEI-sponsored clinical trials.[21,22,23] Best-corrected visual acuity score will be measured at every study visit under standardized lighting conditions by certified study examiners using logarithmic (ETDRS) visual acuity charts, according to the method described by Ferris, et al.[56] Peripheral visual fields in patients with birdshot chorioretinitis will be assessed by quantitative Goldmann perimetry[18] or alternative evaluations of the peripheral field (e.g., automated perimetry using both the SITA-fast 30-2 and the P60, a suprathreshold screening test of the peripheral field).

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